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JOHN WILLIAM GAYLE.

Mr. John W. Gayle, of Frankfort, Ky., Honorary President of the AMERICAN PHARMACEUTICAL ASSOCIATION, was born near Frankfort, September 1, 1859. He became a member of the A. PH. A. in 1891 and by virtue of continued membership is now a Life Member. He served as its vice-president in 1914, and was elected Honorary President at the recent Atlanta meeting.

His early education was received in the County schools, Frankfort City School, Eminence (Ky.) College and Georgetown College. He left college without graduating and taught county schools for three years.

In 1882 Mr. Gayle entered the pharmacy of Joseph LeCompte in Frankfort and became a registered pharmacist by examination in 1884. He is still actively engaged in the retail drug business.

In 1889 he was elected Secretary of the Kentucky Pharmaceutical Association and served in that capacity for fifty consecutive years. On retiring from this position in June 1939 Mr. Gayle was presented with a gold plaque commemorating his half-century of outstanding service and was also made Secretary Emeritus by acclamation.

In 1897 Mr. Gayle was appointed a member of the Kentucky Board of Pharmacy, was at once made secretary and served in that office for forty-one years. Immediately after his appointment to the board Mr. Gayle attempted to have passed a state pharmacy law and during the last hours of the session of the legislature, in 1898, succeeded after most strenuous effort. This was one of the big moments of his life. For twenty-seven years thereafter he was chairman of the Legislative Committee and was successful in having passed every amendment to the state law which the association desired.

Mr. Gayle served as Treasurer of the National Association Boards of Pharmacy for twenty years.

In 1888 Mr. Gayle married Miss Annie Macklin of Frankfort. Two sons and one daughter graced their home, both sons following in the footsteps of their father and becoming retail pharmacists.

EDITORIAL

E. G. EBERLE, EDITOR EMERITUS. E. F. KELLY, ACTING EDITOR.

THE NEW PUBLICATION PROGRAM.

IN ACCORDANCE with its established policy, the AMERICAN PHARMACEUTICAL ASSOCIATION has again modified its publication program with the object of providing satisfactory service to the profession and of keeping in step with progress.

Each year since it was established in 1852, the ASSOCIATION has held an annual meeting with one exception. In 1861, the conditions brought on by the opening of the Civil War made it necessary to omit an annual meeting. From 1852 to 1911, inclusive, the ASSOCIATION issued a Proceedings which was its only regular publication and in which its activities for the year were reported. In order to provide another service the Report of the Progress of Pharmacy, now known as Pharmaceutical Abstracts, became an important feature of the annual Proceedings.

With the establishment of Local Branches in 1905, it became necessary to have a means of more frequent publication, and the Bulletin was issued monthly from January 1906.

In 1911, another important modification was made. The Bulletin became a monthly Journal in which the proceedings of the annual meeting including addresses, reports, papers, etc., were also published and the Proceedings became the YEAR BOOK in which Association data and the Report of the Progress of Pharmacy appeared.

Later, an increasing demand for more frequent publication of abstracts arose and led to the discontinuation of the YEAR BOOK with Volume 24 for 1934. Since that year, Pharmaceutical Abstracts have been published monthly in the JOURNAL, the November issue of which has been made the Proceedings Number, to accommodate the ASSOCIATION data theretofore published in the YEAR BOOK and to condense the proceedings into one issue as a valuable reference volume.

This last change brought the JOURNAL increased and well-merited prestige as a scientific and reference publication. However, the rapid increase in the number of papers, reports, etc., submitted for publication and the expansion of the abstract service made it impossible to give adequate attention to current events in Pharmacy and to provide satisfactory publicity for the rapidly expanding activities of the ASSOCIATION. Moreover, the increased cost of the publication brought a difficult financial problem.

During the last two years, the Council, through its Publication and Finance Committees, has given careful study to a further modification of the publication program to meet these conditions. In the meantime, Editor Eberle found it necessary to retire and Secretary Kelly served as Acting Editor until the modified program could be worked out.

At the recent Atlanta meeting of the ASSOCIATION, the Council gave lengthy consideration to this matter and unanimously adopted a program which it is confidently expected will meet the difficulties referred to in the preceding paragraph and will result in a much more satisfactory service to the members of the ASSOCIATION and to Pharmacy in general.

It was decided to continue the present JOURNAL and to issue on or about January 1, 1940, and under a suitable title, another monthly journal of the same page size to facilitate binding, storage and the interchange of material; to limit in general the material published in the present JOURNAL to scientific articles, reports and abstracts, and to publish in the new journal all other matters; to furnish the present JOURNAL, the new journal or both as determined by replies received upon inquiry, to members of the ASSOCIATION until December 31, 1940, after which time experience may necessitate a change in this arrangement; to send the new journal to all dues-paid members of State Pharmaceutical Associations gratis for a period of one year, after which a subscription price shall be fixed by the Council for those not A. PH. A. members and the journal sent only to bona fide subscribers; to continue the present advertising policy for both publications with such modifications as the Council may find advisable.

Dr. A. G. DuMez who served for several years as the Editor of the YEAR BOOK and since as Editor of Pharmaceutical Abstracts, will also serve as Editor of the present JOURNAL and will have the continued assistance of the Board of Review of Papers which will be expanded as experience indicates to be desirable.

Secretary Kelly will serve as Editor of the new journal and will have the assistance and guidance of an Advisory Editorial Board, the members of which will be chosen with the object of giving representation to the groups most directly interested in the new publication.

It will be recalled that two members of the ASSOCIATION who are interested in the new journal contributed $45,000 to be used to cover the additional cost during the period in which it is being established.

It should be emphasized that the new journal is intended to supplement and not to replace the present JOURNAL; to give publicity to the activities of the ASSOCIATION and to the other important current events in Pharmacy; to furnish editorial comment on matters of importance; and to provide closer coöperation with state and local pharmaceutical associations in the field covered by the A. PH. A. It is expected that the present JOURNAL will be made of greater value to those interested in the scientific phases of Pharmacy and that the new journal will appeal strongly to the practicing pharmacists in every division since it will deal principally with their professional problems and will serve them in promoting professional service.

It is hoped that the new journal will be of real help to the State Associations and their members and that it will assist in bringing about a closer knit professional organization and a more effective national program of Pharmacy.

E. F. KELLY, *Secretary*,
A. G. DUMEZ, *Chairman Publication Committee*.

NATIONAL FORMULARY REVISION.

DURING the decade that closed with the Atlanta meeting, several fundamental changes were made in the process of revising the N. F. These changes were made necessary by the changes in status of the book itself and by medical progress.

The passage of the Federal Food, Drug and Cosmetic Act gave the N. F. as well as the U. S. P. a much more important position in the enforcement of the

Act and also gave the Secretary of Agriculture the power to promulgate standards for drugs if upon request, the appropriate committee of revision did not take action within a reasonable time. These responsibilities will be extended as the states amend their acts to correspond to the Federal act.

Medical progress is now probably greater in one year than it was in a decade when the N. F. was established and the N. F. as well as the U. S. P. must keep abreast of this progress if they are to maintain their present position and render the service expected of them. Formerly, the N. F. was revised over a period of a few years, and after the revision was issued, the Committee on National Formulary was practically inactive during the remainder of the decade. Medical progress now requires that revision be a continuous process.

Admission of drugs and preparations to the N. F. has been based on medical use and in order to have dependable data with respect to medical use, a study of prescriptions was undertaken with the coöperation of the U. S. Bureau of the Census. Later, the U. S. P. joined in this study during which prescriptions were tabulated until new ingredients did not show up. This included about 130,000 prescriptions, carefully selected to secure a dependable sampling, and the results were published in the U. S. P.-N. F. Prescription Ingredient Survey. With this information in hand as to what physicians actually prescribe and use, the revision could be carried out on a sounder basis.

The next step was to extend the scope of the N. F. to include the usable forms of drugs; standards were included in N. F. VI for tablets and ampuls, and studies of other classes of products are being continued. Later, an extensive study in which about ninety experts participated, was made of Materials and Preparations for Diagnostic Use which has resulted in a comprehensive chapter, to be included in N. F. VII, dealing with these preparations which have become of increasing importance since the Federal Food, Drug and Cosmetic Act includes in the description of drugs, those used in or intended for the *diagnosis* of disease.

In 1935, the N. F. Laboratory was established and occupied quarters in the School of Pharmacy, University of Illinois, until it was transferred to Washington in 1938 and became the well equipped A. Ph. A. Laboratory. This unit has demonstrated its great value in N. F. revision in carrying on or coöperating in research and also in carefully checking the accuracy and dependability of standards before their adoption.

It has been customary to elect a Committee on National Formulary each decade and although a few experienced members were reëlected, the wisdom of now providing for a continuous committee, acting as an executive committee of revision, became apparent, as well as for giving auxiliary members a more definite position in revision. Therefore, the By-Law governing the election of the committee was revised at Atlanta to read as follows:

Article V. Committee on National Formulary.—The Committee on National Formulary shall consist of a chairman elected by the Council for a term of ten years and ten members elected by the Council to serve for a term of one, two, three, four, five, six, seven, eight, nine and ten years respectively; each vacancy occurring from expiration of term shall be filled by election for a term of ten years; other vacancies shall be filled by election for the unexpired term. The Committee

shall elect a Vice-Chairman and a Secretary from its own membership. This Committee shall serve as an executive committee of revision of the National Formulary; the members shall serve as chairmen of the sub-committees of the Committee and shall nominate to the Council additional participating members of each sub-committee to the number of not more than five, at least one member of each sub-committee to be a retail pharmacist. The Committee on National Formulary shall report annually, or as often as required, to the Council.

The ten members of the Committee were elected and they are now engaged in selecting the participating members of their respective sub-committees. It was decided by the Council that for the present, the Chairman of the Committee should also serve as Director of the Laboratory on a full-time basis, and located in the headquarters in Washington. This official is now being selected and in the meantime Dr. Gathercoal will continue to serve as Chairman and Director. Provision was also made for an annual meeting of the Committee, just preceding the meeting of the ASSOCIATION, in order that the work of revision might be kept right up to date. This form of organization will, it is expected, enable the Committee to function much more promptly and effectively.

The importance of an arrangement for giving publicity to N. F. revision at regular and frequent intervals and in a form available on a subscription basis to all interested in N. F. revision, became apparent. Those interested should have this information promptly and it is necessary to have their criticisms and suggestions before decisions are reached. To serve these purposes, the Bulletin of the Committee on N. F. was established as a monthly publication in October 1938, on a subscription basis of $5.00, and twelve issues have been devoted exclusively to data relating to N. F. revision. The January issue was devoted to the chapter on Materials and Preparations for Diagnostic Use, the February issue to the revised Monographs for Ampuls, and the August and September issues, in combination, to the monographs approved by the Committee during its recent two-day meeting in Atlanta. In addition, three Correction Lists and one Interim Revision have been issued for N. F. VI.

The grants from the income of the Research Fund and from special funds are now made to outside institutions toward the solution of problems affecting the N. F. and the U. S. P. and this research is carried out under the general direction of the Chairman of the Committee on N. F. working with the Committee on Laboratory. Thus the research work carried on by the N. F. Committee, by the Laboratory and through these research awards is coördinated and directed toward official revision.

To indicate how continuous revision operates under these improved conditions, the N. F. Committee, at its Atlanta meeting, passed upon 162 tentative revisions which represent completed items relating to admissions, deletions and changes in the text since the third Correction List was published January 1, 1939. The retiring N. F. Committee at its final meeting largely completed the revision of N. F. VI in preparation for N. F. VII. This is the first time in the history of the National Formulary that any Committee has prepared two revisions of the National Formulary in one decade. The newly elected N. F. Revision Committee will receive in completed form a very large proportion of the manuscript for

N. F. VII. It also receives numerous problems still in the course of revision. Many of these unfinished problems as well as new proposals which may arise will be passed upon by the new Committee before the completed manuscript of N. F. VII is presented to the Council at the Richmond meeting in May 1940. The ASSOCIATION will then be prepared to proceed with the publication and distribution of N. F. VII. It is hoped that the U. S. P. Convention also will soon be prepared to publish and issue the U. S. P. XII, so that both books will become official in 1941.

The ASSOCIATION intends through these and other changes that may be found advisable, to place the revision of the National Formulary on a sound and effective basis and to enable the publication to serve to the fullest possible capacity, the purpose for which it was originally intended and those which have been developed since that time.—E. F. K.

THE SOUTHERN INSTITUTE FOR HOSPITAL ADMINISTRATORS.

Sessions of the Institute were held at Duke University, July 31st to August 11th, seventy-five, representing all the southern states, participating. The following took part in the program: "Fundamentals of Hospital Organization," James A. Hamilton; "Administrative Aspects of Roentgenology, Pathology and Special Therapy Departments," Robin C. Buerki, M.D.; "Factors Influencing Distribution of Physicians and Hospitals in the South," Wilburt C. Davison, M.D.; "The Medical Staff and Its Administrative Relationships," Robert A. Ross, M.D.; "Surgical and Autopsy Pathology in the Small Hospital," Roger D. Baker, M.D.; "Competition among Hospitals," M. T. MacEachern, M.D.; "Relationship of the Hospital to Public Health," James M. Beeler; "What Is the Cost of Medical Care and Who Can Afford to Pay for It?" F. V. Altvater; "Significance of Group Hospitalization to the South," Abraham Oseroff; "Administrative Problems of the Small Hospital," Miss Macie N. Knapp; "Admitting and Collection Procedures," F. Ross Porter; "The Future of Hospital Administration in the South," W. S. Rankin, M.D.

Tuesday, August 8th, was devoted to a study of the problems of Pharmacy. Dean J. G. Beard, University of North Carolina School of Pharmacy, lectured on, "Pharmacy and Its Place in the Hospital;" and I. T. Reamer, Chief Pharmacist of Duke Hospital, discussed, "Hospital Pharmacy." Two hours were devoted to an inspection tour of Duke Hospital Pharmacy. Demonstrations of the manufacture of safe parenteral fluids as well as many routine pharmaceutical preparations were held for the benefit of the group. Emphasis was placed on the necessity for well-trained pharmacists to handle drugs in the hospital. During the Round Table Discussion many questions were raised regarding the personnel and economy of the hospital pharmacy.

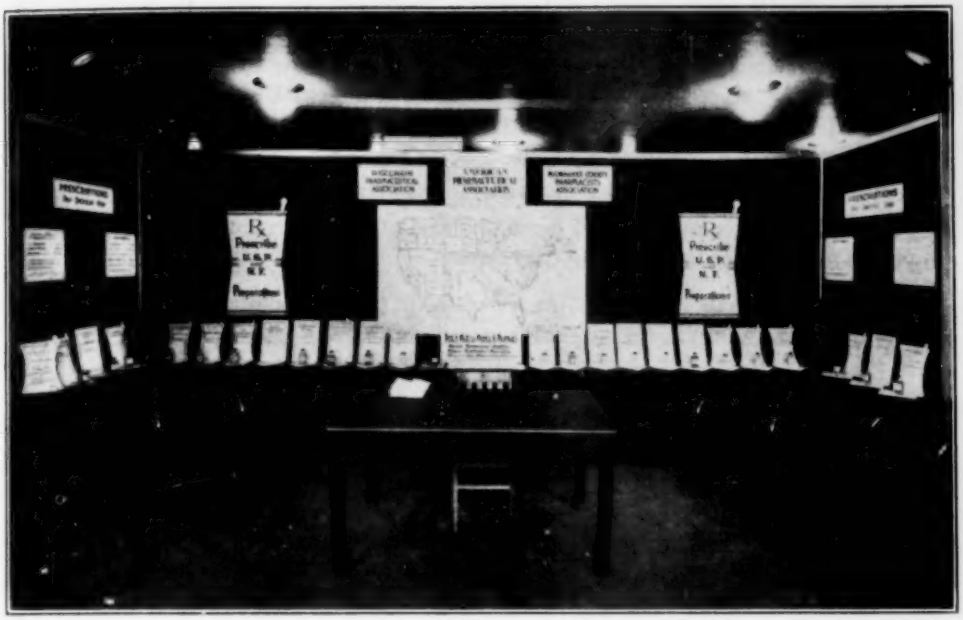
Many administrators were interested in placing pharmacists in their hospitals if they could find suitable trained men. Information regarding interneships in Temple University Hospital, Philadelphia, Pa., and Johns Hopkins Hospital, Baltimore, Md., was given.

Hospitals at various points in the state were visited by the administrators and observations made.

CITIZENSHIP MAY BE REQUIRED IN LICENSURE OF PHYSICIANS.

Citizenship may lawfully be required by the state of Texas of an applicant for a license to practice Medicine, as a condition precedent to the issue of a license, in the opinion of the district court of Travis County, Texas, in a case brought by a citizen of Mexico. Such a requirement was held not to deprive an alien of any right guaranteed him by the federal constitution. As far as available records show, this is the first time that a court has been called on to pass directly on this question. Under the provisions of the constitution a state cannot deny to an alien the right to follow a "common occupation" under the same conditions that it imposes on citizens. The practice of Medicine, the Texas court observed, is not "a common occupation" but is a profession impressed in many instances with semi-official duties.—*Jour. A. M. A.*, Oct. 14, 1939.

AMERICAN PHARMACEUTICAL ASSOCIATION EXHIBIT AT THE AMERICAN DENTAL ASSOCIATION CONVENTION, MILWAUKEE, WIS.



The Annual Convention of the American Dental Association was held in Milwaukee, July 17th to 21st. Sessions and exhibits were at the Auditorium. Pharmacy was represented in the Scientific Section by a 20-foot booth.

Pharmaceutical participation was a coöperative effort between the following Associations: A. PH. A., Wisconsin Pharmaceutical Association and Milwaukee County Pharmacists Association. The following represented these Associations in the order named: Dr. E. F. Kelly, Secretary, Jennings Murphy, Secretary and Emil C. Horn, President. James Hawkins was Chairman and in active charge of the exhibit.

Max Lemberger, State Interprofessional Chairman, and Sylvester H. Dretzka, Board of Pharmacy Secretary, assisted in planning the display. Professor Edward Ireland, of the Pharmacy Faculty of Loyola University of New Orleans, a Wisconsin pharmacist, was the attendant, assisted by Louis Will.

Preparations exhibited were compounded by the faculty members of the University of Wisconsin College of Pharmacy through the courtesy of Dr. Arthur Uhl, Director. The central theme of the display was a large outline map of the United States with the number of dentists and drug stores shown in each State.

The entire exhibit was arranged to bring home the fact that every drug store in the United States is equipped to serve its dentists with the formulas shown and to assist them in prescribing. Emphasis was placed on the fact that a necessary part of drug store equipment is a copy of the U. S. P., N. F. and accepted Dental Remedies.

Visiting dentists were registered at the booth with the object of effecting contacts for the pharmacists of their home localities. It is hoped that this will be a

means of assuring some continuity between the visiting dentists and their pharmacists back home.

Two colored show globes were used. Most of the descriptive cards exhibited were in the familiar mortar and pestle cutout shape to lend a pharmaceutical atmosphere. The Wisconsin Committee suggests that the State populations also be shown as an added feature. THE AMERICAN PHARMACEUTICAL ASSOCIATION furnished leaflets "Notes for the Dentist on Official Medication" for free distribution. These proved popular.

The following points so frequently urged by Chairman Geo. C. Schicks of the A. PH. A. Committee on Dental Pharmacy, and other leaders in this field, were employed to interest dentists visiting the booth:

(1) That it is as important for a dentist to prescribe efficacious medication as it is for him to be adept in the use of his instruments.

(2) That the dental patient is as much entitled to prescription medication as is the patient of a physician.

(3) That a dental patient is entitled to comfort made possible by proper prescribing.

(4) That comfort so given has great good-will building possibilities.

(5) That professional prestige cannot be built by verbal recommendation that the patient purchase certain proprietaries, as per sample given, etc.

(6) That proper medication in the field of prevention is also important.

(7) That if the patient was willing to accept proprietary medication, a trip to the dentist would many times be unnecessary as there is ample offering of this type of medication by radio and the printed page proclaiming their merits to all who will look or listen. The patient evidently needed and wanted something better, or a trip to the dentist would not have been necessary.

(8) That the patient comes to the dentist seeking *specific* treatment.

(9) That if professional prestige is important, no better way could be found than the opportunity offered in the form of prescription writing.

(10) That prescribing is the most *professional* manner of medication because it is a "signed order by the dentist to the pharmacist."

(11) That it is the most *intelligent* because the dentist "knows every ingredient in prescribing."

(12) That it is the most *adaptable* because varying quantities of individual drugs can be employed to meet the varying pathological conditions.

(13) That the fastidiousness of our present-day enlightened public is so changed as to expect the best obtainable from its public health practitioners.

(14) That medication has improved in color, odor and taste.

(15) That dentists should remember that dental treatment is an event "long to be remembered" by the layman, and is not the commonplace experience a professional man may regard it. It behooves the dentist to make the experience as pleasant as possible.

(16) That familiarity with the possibilities of U. S. P., N. F. and Recipe Book preparations will make recommending of proprietary medicines unnecessary.

(17) That pleased patients means more patients.

All dentists contacted appeared enthusiastic as to the possibilities in both the preventative and curative fields which seem to open vast opportunities for coöperation between the two professions.

Besides the exhibit, many drug stores coöperated by devoting their windows to dental displays. Placards, calling attention to this big dental meeting were furnished by the State Pharmaceutical Association and posted in drug store windows.

It was estimated that 8000 dentists were in attendance.

SYLVESTER H. DRETZKA, *Secretary*,
Wisconsin Board of Pharmacy.

Dr. E. N. Meuser of Chengtu, West China, writes interestingly of a proposed College of Pharmacy Building, West China Union University, at Chengtu, Szechwan, China.

The main building is to be a three-story construction of brick and stone, 50 feet by 150 feet in size. The accompanying dormitory for staff, students, etc., as planned, will be a two-story construction, brick and stone, size 40 feet by 120 feet.

Dr. Meuser is appealing for a sum of $7000.00, which, at the present rate of exchange, will provide sufficient Chinese currency to pay for the erection of both buildings as well as the main furnishings for them. To those who are good enough to respond to his specific and urgent appeal, but who may not be clear as to the best method of sending this money to him, he suggests that the money be forwarded to any one of the following:

1. Dr. G. A. Garside, Executive Secretary, Associated Boards for Christian Colleges in China, 150 Fifth Ave., New York City, U. S. A.

2. Dr. J. H. Arnup, General Secretary, Board of Foreign Missions, United Church of Canada, 299 Queen Staw, Toronto, Canada.

3. A Bank Draft may be purchased at your own bank payable through the Bank of China, Chengtu, China, to either the Bursar of the West China Union University, Chengtu, China, or to E. N. Meuser, at the same address.

If the money is sent to either Dr. Garside or Dr. Arnup it should be specifically stated that it is for the Pharmacy Building at Chengtu and it should be forwarded by the earliest and fastest air-mail service, so as to enable them to get the advantage of the present very favorable rate of exchange.

The Philadelphia College of Pharmacy and Science began its 119th session September 13 with entering classes made up of young men and women from every section of the United States and several foreign countries. The entering class is the largest in the past seven years. At the opening day exercises the freshmen were welcomed by President Wilmer Krusen and members of the faculty.

At the conclusion of the exercises the entering students were taken by their faculty advisers on a tour of the College buildings to familiarize them with the equipment and facilities. Later they were guests of honor at a reception tendered by the Women's Club of the Philadelphia College. Mrs. Edgar J. Young was chairman of the committee in charge.

ELMER WILLIAM REBOL.

Elmer William Rebol, the winner of the Fairchild Scholarship, 1939, was born in New Castle, Wash., November 26, 1917, and has lived in Cleveland, Ohio with his parents since 1923. Prior to 1923 he lived for a while in Renton, Wash., and approximately one year in Ljublania, near the Sava River, in Yugoslavia.

Mr. Rebol's father, and later his mother, came to the United States from Yugoslavia. The father is interested in mechanics and has given considerable attention to internal combustion engines, especially the Diesel, and at present is engaged in work which requires skill and knowledge of mechanics. The son in this respect is resourceful and exhibits more than average ability as a neat and careful workman.

After completing an elementary and secondary education, having graduated from Collingwood High School in Cleveland, Ohio in 1934, Mr. Rebol entered Cleveland College of Western Reserve University where he completed their Freshman course in Chemistry, spending the remainder of his time as an apprentice in a drug store. He entered Ohio Northern University College of Pharmacy in September 1935, and after pursuing their required and certain optional courses in Pharmacy, graduated on June 4, 1939, receiving the degree of Bachelor of Science in Pharmacy with high distinction.

Mr. Rebol never exhibited much interest in minimums or grades, always assuming that if he did his work well he need not worry about grades. It is interesting to note that early in 1937 he discovered that certain courses in which he had special interest would be offered during the summer session of the College of Liberal Arts. He immediately made arrangements for his admission to these courses. In the summer session he completed nineteen credit hours (quarter plan) and earned forty-three quality points. At the time of his graduation he had 209 credit hours of college work and 528 quality points. The credit hours and quality points of an average student would have been equal. Being eligible as a candidate for registration as a pharmacist in Ohio, he was admitted to the examination for registration by the Ohio Board of Pharmacy in June 1939 and was successful.

The subject of this sketch is not a conventional bookworm. During his High School and College career he exhibited interest in extra-curricular activities. While in high school he participated in track, glee club, choral society and science club. During his residence in college he was a member of the Men's Glee Club for more than a year, captain and then student instructor in fencing, vice-president and then president of the Ohio Northern University Pharmaceutical Association, a student organization in the College of Pharmacy and rendered valuable service in the University Student Health Service Dispensary.

GUILFORD C. GROSS.

Mr. Guilford C. Gross, winner of the Kilmer Prize for 1939, was born in Bowdle, South Dakota, June 8, 1917, the son of Henry C. and Elsie Lueck Gross, both of whom are living.

His early education was received in the public schools of Bowdle, having graduated from the High School there on May 23, 1935, the highest ranking student in his class. During his high school years he was active in music and sports.

On June 5, 1939, Mr. Gross graduated with honor from the South Dakota State College, ranking senior in a class of one hundred eighty-six. He passed the State Board of Pharmacy examinations with the highest rating of the group represented this year. His retail experience was gained at Gerken Pharmacy, Plankinton, S. Dak.

Mr. Gross was secretary of Rho Chi, 1938–1939; member of the Board of Control and member of Blue Key (men's honorary society). At present he is a graduate student at South Dakota State College, Division of Pharmacy.

At the recent convention of the AMERICAN PHARMACEUTICAL ASSOCIATION in Atlanta the formal presentation of the Kilmer Prize took place, Dr. Heber W. Youngken, chairman of the committee, having been chosen for this occasion. He elaborated on the wonderful work of Dr. F. B. Kilmer, who made the award possible, mentioning his studies on drug plant cultivation, his medicinal plant garden at New Brunswick, N. J. and the many papers which he contributed to scientific organizations on medical plant cultivation. He also made mention of the fact that Dr. Kilmer, in his will, bequeathed a fund of $3000.00 to the A. PH. A., the interest of which is to be kept in trust for the awarding of the Kilmer Prize. This prize is to be granted for the most meritorious paper submitted to the Committee along the line of some phase of Pharmacognosy, preferably in vegetable drugs. After a very careful study of papers submitted this year the Committee decided unaminously in favor of the one of Mr. Gross, on "A Study of Red Squill." The Prize is a gold key, bearing on one face the likeness of Dr. Kilmer together with the Greek words φαρμακογνωσις meaning pharmacognosy. On the opposite face the name of Dr. Kilmer, the dates of his birth and passing, together with the Kilmer Award, the name of the recipient and the date of presentation, the same being representative of the feelings of Dr. Kilmer and the AMERICAN PHARMACEUTICAL ASSOCIATION toward an individual who has presented outstanding work.

Mr. Gross made the trip from South Dakota to Atlanta to receive the award. His accomplishments in the past give promise of more and greater things to come, and the good wishes of all go out to him for success in the future.

SECTIONS

BOARD OF REVIEW OF PAPERS (SCIENTIFIC SECTION).—*Chairman*, F. E. Bibbins; H. M. Burlage, J. L. POWERS, E. V. Lynn, C. O. Lee, L. W Rising, L. W. Rowe, Heber W. Youngken, Ralph E. Terry, Carl J. Klemme

A PHARMACOGNOSTICAL STUDY OF THE PARATHYROID. I.*

BY HEBER W. YOUNGKEN.[1]

The parathyroid glands occur in all vertebrates except fishes. Those of cattle, sheep, hogs, horses and some other mammals including man have been found to secrete a water-soluble, thermostable hormone. This has been extracted from the parathyroids by Hanson and Collip as a preparation containing the hormone and is found to relieve the symptoms of parathyroid tetany and to increase the calcium content of the blood serum in man and laboratory animals.

Two common forms of preparations of the parathyroid occur in drug channels to-day, namely Solution of Parathyroid (Parathyroid Extract) and Powdered Desiccated Parathyroid (Parathyroid Powder). Both of these have been used in medicine in conditions in which the blood calcium is below normal, such as tetany in infants, certain cases of malnutrition, paralysis agitans, etc., their administration being controlled by frequent examination of the blood for calcium. The solution is largely preferred.

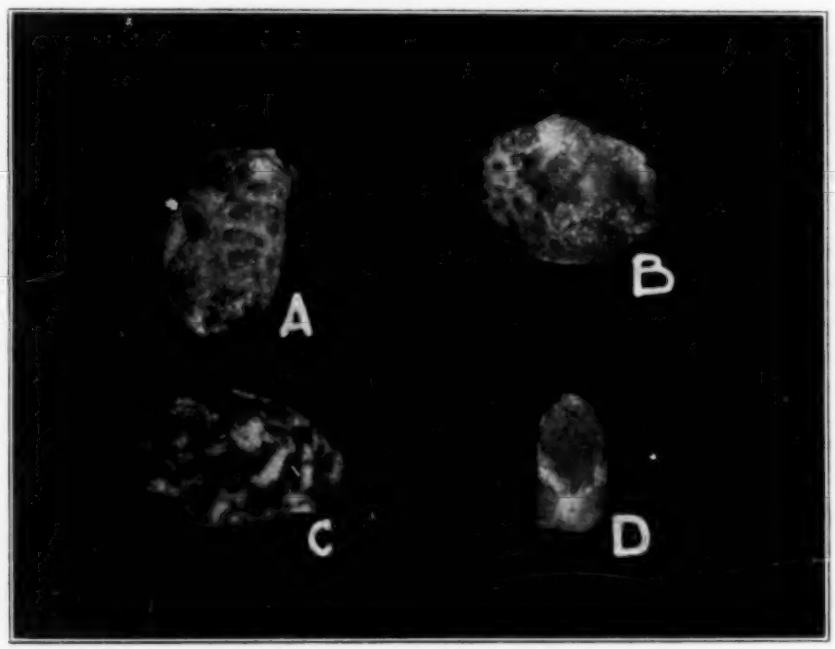


Fig. 1.—Parathyroid Glands of Cattle, × 1 1/8. A, Gland showing inner surface. B, Gland showing outer surface. C, Longitudinally halved gland showing cut surface. D, Transversely cut section of gland. The white areas in C and D represent connective tissue trabeculæ which divide the parenchyma of the gland into somewhat poorly defined lobules.

* Presented before the Scientific Section, A. PH. A., Atlanta meeting, 1939.

[1] Massachusetts College of Pharmacy, Boston, Mass.

The raw material from which these medicaments are prepared consists of the fresh parathyroids of healthy domesticated animals used for food by man. At the present time cattle appear to yield most of it.

Owing to certain similarities existing between powdered desiccated parathyroid and thyroid and the relatively higher cost of production of the former, and also because of the close anatomical relationship of these glands in animals, it is conceivable that powdered parathyroid could readily be adulterated with thyroid and that either product might be admixed with the other without detection unless some means of microscopical differentiation were available.

The chief aim of this investigation, therefore, was to endeavor to find a method whereby parathyroid powder might be distinguished from powdered thyroid microscopically or microchemically. Other objectives were to describe the whole and powdered desiccated parathyroids of cattle.

The literature on the pharmacognosy of the parathyroid is very meager. Considerable, however, has been written on the action and uses of extracts of this gland.

In 1855, Robert Remak (1), a German physiologist and embryologist, first discovered the parathyroids. In 1880, Ivar Sandström (2), a Swedish anatomist, established their occurrence in the dog, cat, ox, horse, rabbit and man and published a description of them limiting a detailed description to those of man. He believed them to represent displaced, undeveloped fragments of thyroid tissue. In 1891, Gley (3) demonstrated that they functioned independently.

In 1897, E. Gley (4) published a paper on the effects of extirpating the thyroid glands in the dog and rabbit wherein the animals were shown to develop the symptoms of parathyroid tetany, a condition marked by violent convulsions. This condition was shown to be relieved temporarily by the intravenous injection of calcium salts.

Until the early part of the twentieth century, however, only very brief consideration of these glands was given in the anatomical works. One of the earliest anatomical textbooks to give a good description of the human parathyroid glands including their histology was Piersol's "Human Anatomy" (5) published in 1907 which contains photomicrographs illustrating their inner structure. More extensive treatment of the histology of the human parathyroid has been given in later works on histology, especially those of Maximow and Bloom (6) and Bremer (7).

In 1932, R. Wasicky (8) briefly described the parathyroid glands and the preparation of the extract and stated their location in the horse, cattle, sheep and hogs. The same author in his "Leitfaden für die Pharmakognostischen Untersuchungen" briefly described and figured a teased-out preparation of the fresh parathyroid (9).

MATERIALS AND METHODS.

The materials studied included whole fresh and desiccated parathyroid glands of beef, and powdered desiccated parathyroid and thyroid glands of beef. The whole glands were examined *in situ*. A number of whole glands were fixed and preserved in formol-alcohol and in formol-acetic-alcohol. Segments of these were later dehydrated and imbedded in paraffin, and later sectioned, stained and mounted in balsam for microscopical examination. A variety of single and double stains were employed as well as chemical reagents which will be discussed later in this paper under the description of the sections and the powdered materials.

The powdered desiccated glands were variously treated with a number of single and double stains on slides, in watch glasses and by the centrifuge method, all of the stains excepting Mallory's

and phosphotungstic acid being diluted with water. In the watch-glass method, the powder was placed in a Syracuse watch glass, the diluted stain introduced and allowed to act for a variable length of time depending upon the stain or reagent used. By means of an eye dropper, the stain was removed and any excess washed out of the powdered fragments by water or alcohol. It was necessary to place the watch glass containing the stained powders on the stage of the microscope in some instances and examine the effect of the stains in order to prevent over- or under-staining. After staining, the powder was either transferred to a clean slide and mounted for microscopic examination in water or glycerin solution or run through 50%, 70% and 95% alcohols, followed by clove oil and xylol and mounted in balsam as a permanent mount.

By the centrifuge method, a portion of powder was placed in a clean centrifuge tube, the diluted stain introduced and the mixture centrifuged for several minutes. The tube was then removed from the centrifuge, and the stain decanted from the powder packed at the bottom, water introduced into the tube and the contents again centrifuged in order to wash out excess of stain, and the washing decanted. With some stains it was necessary to employ several washings of water for the removal of excess stain. The powder was then centrifuged successively with ascending grades of alcohol through absolute alcohol and xylol, the xylol mostly decanted and powder removed by a pipette and mounted in balsam for microscopic examination. The stained sections and powders were studied under a biological microscope equipped with a 10 × ocular and with 16 mm., 4 mm. and oil-immersion objectives.

The glandular materials used in this investigation were supplied generously by Armour & Co., the Wilson Laboratories and Parke, Davis & Co., to whom my thanks are due.

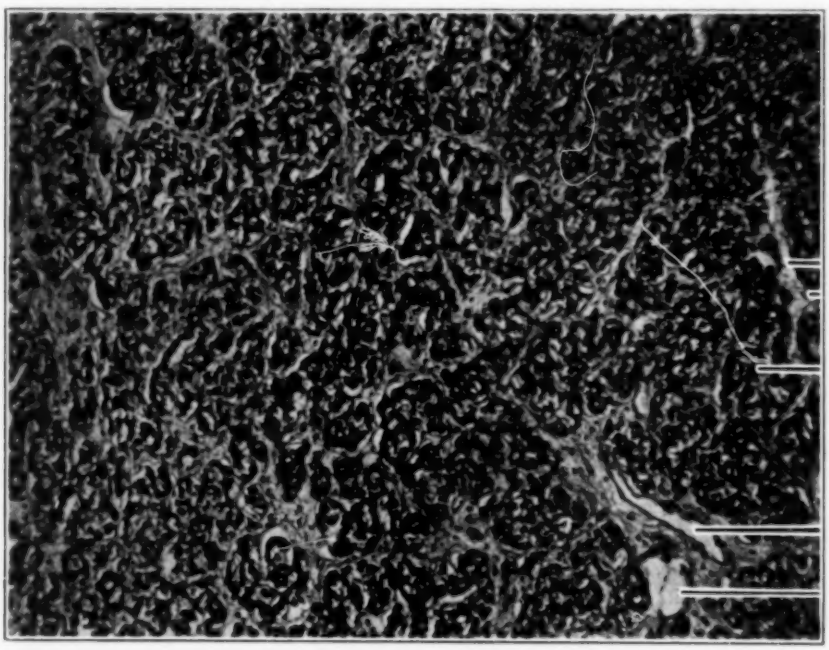


Fig. 2.—Representative Portion of a Transverse Section of the Parathyroid Gland of Cattle, ×100. Note the dark-colored anastomosing columns of epithelial cells (ep), surrounded by light-colored, reticular connective tissue (ct) containing a capillary network. c, longitudinal sections of capillaries; f, fat tissue. The section was stained with hematoxylin and eosin.

DESCRIPTION OF WHOLE PARATHYROIDS OF CATTLE.

The parathyroid glands of cattle are small, red or yellowish, oval, elliptical or pyriform bodies situated near the ventral border or toward the middle of the posterior surface of the lateral

lobes of the thyroid. They are claimed by embryologists to be produced by the third and fourth pharyngeal pouches as epithelial (entodermal) bodies which become attached during development to the posterior surface of the thyroid gland. Those examined by the writer were up to 2 8 cm. x 1.5 cm. x 0.8 cm. They were lying in connective tissue on the surfaces of the lobes of the thyroid, not imbedded in the surface or attached to it by pedicles as in some other animals. Each was surrounded by a fibrous capsule of connective tissue which supported blood vessels. (See Fig. 1.)

The whole desiccated parathyroids examined occurred in plano-convex pieces, representing longitudinally sliced halves, rarely as bean-shaped entire glands from 1 to 2.7 cm. in length, from 0.8 to 1.4 cm. in breadth and from 0.4 to 0.7 cm. in thickness; externally pale yellow, with brown blotches, dull and waxy and showing on the convex surfaces irregular depressions, lines or ridges, the latter on some glands appearing like blisters; texture spongy and oleaginous; internally pale yellow, waxy and oily with irregular cavities; odor suet-like; taste oily and saponaceous.

HISTOLOGY OF THE PARATHYROIDS OF CATTLE.

Transverse sections exhibited an outer zone of loose connective tissue in which were imbedded sections of blood vessels and which surrounded the main body of the gland composed of numerous epithelial cords disposed as solid masses and branching columns. Between the cords was to be noted a framework of reticular fibers and here and there sections of sinusoidal capillaries, some containing blood corpuscles. (See Fig. 2.) The capillaries form a veritable network in the parenchyma. Some of the capillaries were in close relation to the epithelial cells of the cords. Scattered through the gland were many areas of fat tissue. Fat globules were visible in many of the epithelial cells in teased-out preparations.

The epithelial cells were polygonal to rounded polygonal and varied considerably in size. There appeared to be several types of these, the principal, oxyphil and intermediate types. The principal type possessed large nuclei of varying shape, chiefly spheroidal, oval, oblong or irregularly fusiform and pale clear cytoplasm. The oxyphil type differed from these in being somewhat larger and in possessing numerous granules in their cytoplasm which were stained red in sections stained with hematoxylin and acid fuchsin. They resembled the oxyphil cells depicted by Maximow and Bloom (6). Other epithelial cells of the cords showed characters intermediate between the principal and oxyphil types. The epithelial cells formed dense masses and anastomosing columns. Occasional acini (follicles) were observed in some of the sections, but only in one out of a large number of glands sectioned by the writer was colloid observable and this was not abundant. Colloid has been reported in the acini or follicles of the human parathyroid by Maximow and Bloom (6) and by Bremer (7). It appears to be the result of degenerative changes in the organ and not a normal constituent of it.

With equal parts of Mallory's stain and 1% phosphotungstic acid solution the epithelial cells were stained brown, the connective tissue fibrils a deep blue and the other connective tissue elements a bluish green to blue, the walls of the arterioles blue.

With Delafield's hematoxylin and eosin the nuclei of the epithelial cells were colored blue, the cytoplasm of these purple to pinkish-purple, the connective tissue, including the reticular fibers, faintly pink and the nuclei of the connective tissue cells, blue.

With copper hematoxylin and eosin the effect of the staining was similar, but sharper.

With Delafield's hematoxylin and acid fuchsin, the nuclei of the epithelial cells were colored blue to purple, the cytoplasm red to deep pink and the cytoplasmic granules of the oxyphil cells and intermediate cells (containing smaller granules) appeared pink and refractile.

With Weigert's hematoxylin and acid fuchsin, the nuclei of the epithelial cells were colored blue, the cytoplasm purple and the cytoplasmic granules of the oxyphil and intermediate types, purple to red. The reticular fibers were colored pinkish-purple to purple, the nuclei of connective tissue cells, blue.

An examination of sections of the thyroid gland of cattle stained with Delafield's hematoxylin and eosin and with Mallory's stain and phosphotungstic acid showed striking differences from the parathyroids of the same animal. In the thyroid numerous follicles containing colloid and lined by epithelial cells of one type and separated from each other by narrow strands of reticular connective tissue were apparent. This contrasted sharply with the solid masses and anastomosing columns of epithelial cells and the total absence of follicles containing colloid in most of the sec-

tions of parathyroid. Moreover, the reticular tissue between the follicles of the thyroid appeared averagely less abundant than between the masses and columns of epithelial cells in the parathyroid. Further, at least three types of epithelial cells were observed in the sections of parathyroid, whereas only one type of these was clearly discerned in the thyroid.

POWDERED DESICCATED PARATHYROID OF CATTLE.

The samples of powders examined varied in color from pale yellow to light buff. When treated with Mallory's stain and 1% phosphotungstic acid solution, equal parts, the epithelial cells were colored yellow through orange to brown, depending upon the thickness of the fragments, the connective tissue blue to greenish-blue. Reticular fibers were noted in some of the mounts projecting from fragments of epithelial cells and appearing curved.

With Bismark Brown, 0.5% sol. in 50% alcohol, diluted with an equal quantity of water, the cytoplasm of the epithelial cells was stained varying shades of yellow and brown while the cytoplasmic granules appeared globular and refractile. The connective tissue appeared yellow to brown in this stain.

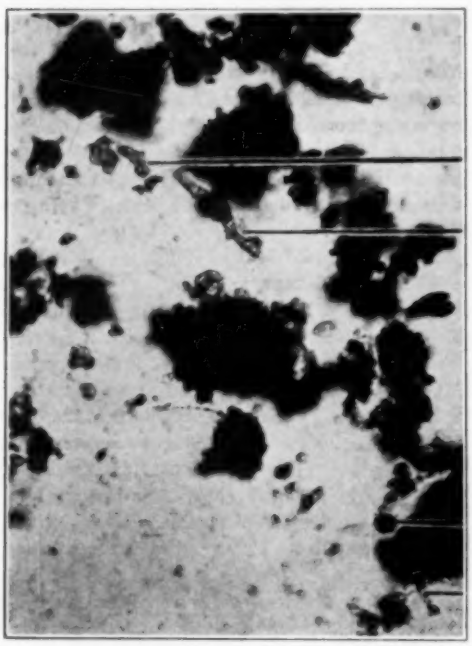


Fig. 3.—Powdered Desiccated Parathyroid. Photomicrograph, ×200. ep, epithelial cells; v, blood vessel; c, connective tissue fiber with attached epithelial cells. The dark masses represent fragments of the parenchyma of the gland, from some of which reticular fibers are seen to project. ep′, small mass of epithelial cells with two reticular fibers projecting from upper portion.

With diluted Delafield's hematoxylin the nuclei of the epithelial cells were colored blue, the cytoplasm purple, the connective tissue fibers light purple. The epithelial cells measured up to 12 microns in diameter.

With Weigert's hematoxylin and acid fuchsin, diluted with an equal amount of water, the nuclei of the epithelial and connective tissue cells were colored blue, the cytoplasm pink and the fibers red, pink or pinkish-purple.

With equal parts of a mixture of Delafield's hematoxylin, eosin and water, to which a drop of glycerin was added before applying the cover slip, the epithelial cells were colored pinkish-purple to purple in their cytoplasm and cytoplasmic granules were brought out very distinctly. The connective tissue fibers were stained pink to pinkish-purple. In only one of many mounts examined, two fragments of colloid were detected which were stained pinkish-purple. The same amount of powdered beef thyroid similarly stained and mounted showed numerous colloid fragments.

In contrasting the microscopic picture of powdered parathyroid with powdered beef thyroid, it was found that colloid fragments are common and abundant in all mounts of thyroid whereas they were unusual in parathyroid material examined and only detected once after examining a large number of mounts. Other means of distinguishing between powdered desiccated thyroid and parathyroid were also tried.

It was found that when a small amount of powdered desiccated thyroid was sprinkled on the surface of water, it almost immediately sank. When the same procedure was tried with powdered desiccated thyroid, the particles floated for a long time. This can be attributed to the fact that parathyroid contains considerable fat while thyroid does not.

The color reactions produced by treating the two powdered glands with various chemicals in white porcelain dishes proved interesting. When about 5 mg. of each drug were treated with 2

or 3 drops of a reagent consisting of equal volumes of 5% alcoholic solution of vanillin and concentrated HCl, powdered thyroid was colored brown and powdered parathyroid pinkish-brown changing to pink. Solution of NaOCl colored thyroid tan-brown and parathyroid yellow. Millon's reagent colored thyroid reddish brown and parathyroid light reddish-brown. While the color tests are helpful, they are not conclusive in determining the identity of the material. Further studies are contemplated especially to determine other microscopic differences between these powdered endocrine glands.

SUMMARY.

1. The history of the parathyroid is reviewed.

2. A description is presented of the whole fresh and whole desiccated parathyroid glands of cattle.

3. The histology of the bovine parathyroid and the appearance of its cells after treatment with various stains are described.

4. It is shown that follicles are relatively few in sections of the parathyroids of cattle and that numerous solid masses and anastomosing cords of epithelial cells separated by reticular tissue rich in capillaries make up the bulk of the parenchyma, whereas in sections of the thyroid of the same species follicles surrounded by connective tissue containing capillaries make up the greater portion of the parenchyma while occasional masses of epithelial cells (interfollicular epithelial cells) were relatively few.

5. All the follicles of the thyroid of cattle contained colloid and this material represented the most conspicuous element present, whereas only occasional colloid-containing follicles were present in the parathyroid.

6. Several types of epithelial cells occurring in the bovine parathyroid are described. Only one type was noted in the bovine thyroid.

7. The results of the study of powdered desiccated parathyroid of cattle are presented. It was found that colloid fragments were unusual and exceedingly rare in the materials examined, whereas these occurred as the most conspicuous elements in the powdered thyroid of this and other species recorded.

8. Several qualitative color tests for powdered parathyroid and thyroid are described.

REFERENCES.

(1) Remak, R., "Untersuchungen über die Entwicklung der Wirbelthiere," *Ebenda*, Berlin 39–40; 122–124 (1855).

(2) Sandström, I., "On a New Glandule in Man and Several Other Mammals," *Upsala Lakaref Förh.*, xv, 31 pages (1878–1880).

(3) Gley, E., "Sur les functions du corps thyroid," *Compt. rend. soc. biol.*, 42, 841–847 (1891).

(4) Gley, E., *Compt. rend. soc. biol.*, 49, 18 (1897).

(5) Piersol, G. A., *et al.*, "Human Anatomy," 1795 (1907).

(6) Maximow, A. A., and Bloom, W., "A Text Book of Histology," 3rd Edition, 304–306 (1938).

(7) Bremer, J. L., "A Text Book of Histology," 426–427 (1930).

(8) Wasicky, R., "Lehrbuch der Physiopharmakognosie für pharmazeuten," II Teil, 593–595 (1932).

(9) Wasicky, R., "Leitfaden für die Pharmakognostischen Untersuchungen," 391 (1936)

THE ASSAY OF DIGITALIS.*,[1]

I. Criteria for Evaluating Various Methods Using Frogs.

BY LLOYD C. MILLER, CHESTER I. BLISS[2] AND HERBERT A. BRAUN.

An important problem in bioassay is to minimize the variations which seem to be inherent in the responses of living organisms. In the bioassay of digitalis, using frogs, numerous modifications in the technical procedure have been advocated toward this end. Length of the period of observation, weight, sex and species of the frogs, volume and alcoholic content of the injected material, environmental temperature, all these and other factors have been varied by the many who have worked in this field.

Adoption of certain restrictions may possibly bring about a reduction in the variations associated with the present official method. All will agree that such adoption should be based upon a critical examination of the results of well-planned experiments. With the preparation of the twelfth revision of the United States Pharmacopœia scheduled to begin next year, it seems likely that the assay of digitalis will be the subject for considerable investigation in the near future. At present there exist no generally accepted criteria by which the results of such studies can be evaluated objectively. The purpose of this paper is to present certain criteria which should meet this need and it is hoped that their availability will encourage the designing of experiments in a manner that will permit their application.

As a first prerequisite it is suggested that all investigators test their proposed modification of the method on some standard material, preferably a uniform preparation of powdered digitalis. In view of the adequacy[3] of the supply of U. S. P. XI Reference Digitalis Powder, this is probably the best one for all to use. The comparability of the results on the same standard for each particular proposal will furnish the first step in bringing the data of all laboratories to a common meeting-ground. A second prerequisite is still more important to guarantee fully the desired result and that is to plan each experiment so that it will be self-contained. Only in this way can the experimental error be calculated satisfactorily and the results evaluated objectively. To supply this essential internal check, each modification in procedure should be tested at more than one dosage level of any given material. Thus if the variation in the amount of alcohol in the test material is suspected of influencing the assay, tests should be run in parallel with two or more concentrations of alcohol, each at two or more dosage levels. This will permit the construction of a dosage-effect curve for each concentration of alcohol tested and

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[3] Prof. E. Fullerton Cook, Chairman of the U. S. P. XI Revision Committee, has indicated that there is ample U. S. P. XI Reference Digitalis Powder available; less than one-fifth of the original supply has been distributed in the three years since its adoption.

(Note added in press.)—At the conference on the Assay of Digitalis held at Atlanta, Ga., August 23, 1939, it was decided that the unusually high potency and possibly other characteristics of the U. S. P. XI Reference Digitalis Powder made it less suitable for use in collaborative investigations than a composite powder more nearly like the average digitalis of commerce. Such a composite is being prepared for the projected collaborative U. S. P. study.

will afford a means of estimating the experimental error associated with the comparison. It cannot be assumed that this error will remain constant, even from one day to the next, so that no serious comparisons should ever be attempted on the basis of this assumption.

When comparative data have been obtained, as, for example, on two modifications of the procedure, a method of computation is needed that will extract from the results all of the relevant information. In the following sections a method of computation is outlined by which certain informative characteristics or parameters can be obtained from the data and the criteria to be presented involve comparisons of these parameters. If the data of all investigations are such as to permit drawing these comparisons, the result will be a tremendous simplification in the task of coördinating the results and deriving from them objective evidence on which decisions regarding the U. S. P. XII monograph for the assay of digitalis can be based.

THE DETERMINATION OF RELATIVE POTENCY.

The classical work of Trevan (1) forms a starting point for the consideration of a suitable procedure. It is rather generally known from his study that an S-shaped curve is obtained when the percentage of frogs showing positive effects of digitalis is plotted against the dosage. Less generally known is the fact that the same data can be transformed into a straight line. This transformation involves plotting the logarithm of the dose against an expression of the percentage effect in units derived from the normal frequency curve. These units were first suggested in a form suitable for computation by Gaddum (2) ("N. E. D.") and later by Bliss (3) in the somewhat more convenient "probits." Tables of probits may be looked upon in the same light as tables of logarithms, which are so familiar that most people use them without concern as to their derivation. This fact may encourage those who hesitate to adopt the percentage-to-probit transformation prior to becoming acquainted with its theoretical basis, which has been described elsewhere (4). The determination of the dosage-effect curve from small numbers of animals has been treated in detail in a recent publication (5). The computation of the basic curve may be reviewed by means of a numerical example.

Experimental Details.—Male frogs weighing from 17 to 30 Gm. were distributed into groups of five in the assay tank which was maintained at 19.6 ± 0.2° C. By preliminary trials, two series of three doses of digitalis were selected such that their logarithms were equally spaced, one or two digit numbers. They were prepared from a tincture of U. S. P. XI Reference Digitalis Powder (0.0745 Gm. per cc.) and assigned to the groups of frogs at random so that six groups, or thirty frogs, received each dose from each series. One series of doses was contained in a volume of 0.01 cc. per Gm. and was injected intramuscularly, dividing the dose between the two thighs as suggested by Dooley and Higley (6). The second series, contained in 0.02 cc. per Gm., was injected into the ventral lymph sac. One-half of the frogs receiving each series of doses were pithed and examined one hour after injection, while the remaining frogs were pithed and examined after

TABLE I.—INFLUENCE OF ROUTE OF INJECTION ON POTENCY.

U. S. P. XI Reference Standard Digitalis Given Intramuscularly and by Lymph Sac in One-Hour Method.

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Route.	Dose, *Cc./Kg.*	Log-Dose. *x.*	Result.	%	Empirical Probit.	Expected Probit. *Y.*	Corrected Probit. *y.*	Weight. *w.*	Products. *wx.*	*wy.*
Lymph Sac	5.62	.75	2/15	13.3	3.889	3.93	3.891	6.22	4.6650	24.20202
	7.08	.85	5/15	33.3	4.569	4.53	4.570	8.81	7.4885	40.26170
	8.91	.95	8/15	53.3	5.084	5.13	5.084	9.49	9.0155	48.24716
Intra-Muscular	2.82	.45	2/15	13.3	3.889	3.86	3.892	5.86	2.6370	22.80712
	3.55	.55	5/15	33.3	4.569	4.64	4.571	9.11	5.0105	41.64181
	4.47	.65	10/15	66.7	5.431	5.41	5.430	8.98	5.8370	48.76140

an interval of four hours. Thus the complete experiment or "assay" involved four dosage-effect curves, showing the reaction after one hour to digitalis injected in the lymph sac and injected intramuscularly, and after four hours to the same two modes of injection. For present purposes only the one-hour results will be considered.

Computation of the Dosage-Effect Curve.—The data and the first stages of the computation are given in Table I. Column 1 indicates the route of administration of the doses of digitalis listed in column 2, the logarithms of which (x) are in column 3. Column 4 lists the fractions representing in the denominators the total number of frogs injected and in the numerators the number showing systolic standstill at the time of observation. The results have been changed to percentages in column 5 and to the probits corresponding to these percentages in column 6. The next step in the procedure is to plot the corresponding entries in columns 3 and 6 against each other on cross-section paper (Fig. 1). Each set of points can be fitted by eye with a straight line (not shown in the figure) which represents the first approximation to the relation between dose and effect under the two conditions of the experiment, namely, intramuscular and lymph sac injection. Each such line is the best graphic estimate of the relation that one would expect to find if an infinitely large number of similar frogs could be used in a single test. Provisionally, then, it can be looked upon as the *expected* relationship, and for each dose there is a corresponding *expected* probit.[1] The expected probits (Y, column 7) are used to enter appropriate tables[2] (7, 8) to obtain both the corrected probit (y, column 8) and the weight (w, column 9), which also depends on the number of frogs used, to be assigned to each observation. In columns 10 and 11, the respective products of wx and wy are tabulated.

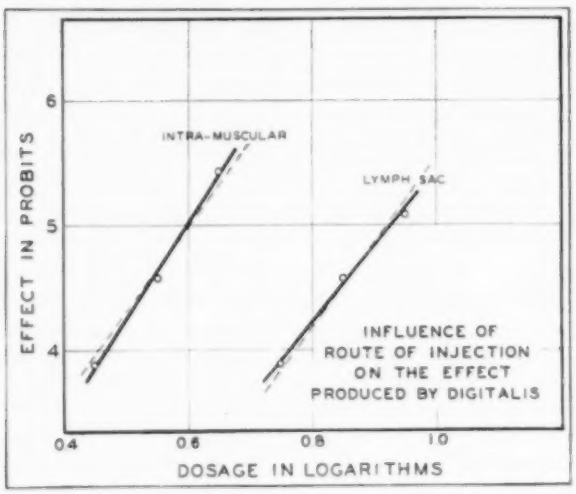

Fig. 1.

From these values it is possible to compute the first calculated approximation, which is usually sufficient, by formulas which are reproduced for convenience in Table II together with the numerical terms computed from the data in Table I.

The parameters listed in Table II are the basic units defining each dosage-effect curve and will be used subsequently in several combinations. The position of the best-fitting straight line for any single series is determined by the weighted mean probit ($\bar{y}$) at the weighted mean log-dose ($\bar{x}$), through which point the line will pass with a slope given by b. These computed curves have been plotted as solid lines in Fig. 1. If the experiment is conducted so that the frogs receiving the different doses are really equivalent in susceptibility, the observed probits should differ from the computed line only by chance. This is checked by the last term in Table II, χ^2 ("chi-square"), which shows whether or not the variation is too great to be considered due to errors of sampling. When χ^2 exceeds the limit for $P = 0.05$ (9) there is less than one chance in twenty that the frogs used at the different dosages were really equivalent and not much importance can be attached to the results of so erratic a test. With the proper experimental precautions, however, χ^2 usually

[1] The expected probits may be read directly from the graph if only three or four doses are used in the experiment. With a larger number of doses it is probably more rapid to calculate the expected probits as suggested elsewhere (5).

[2] Expanded tables giving the corrected probits in terms of the expected probits with a minimum of interpolation for all possible results in groups of twenty animals or less have been prepared in mimeograph form and are available, upon request, from the Division of Pharmacology, Food and Drug Administration.

TABLE II.—PARAMETERS OF DATA IN TABLE I.

Parameter.	Formula.	For Lymph Sac Curve. "Standard"		For Intramuscular Curve. "Unknown"
$S(w)$	(Sum of Col. 9)		24.52	23.95
$S(wx)$	(Sum of Col. 10)		21.1690	13.4845
$\bar{x}$	$\frac{S(wx)}{S(w)}$	$\frac{21.1690}{24.52}$	= .8633361	.5630271
$S(wy)$	(Sum of Col. 11)		112.71088	113.21033
$\bar{y}$	$\frac{S(wy)}{S(w)}$	$\frac{112.71088}{24.52}$	= 4.5966917	4.7269449
$[wx^2]$	$S(wx^2) - \bar{x}\,S(wx)$	18.42870 − .8633361(21.1690)	= .152738	.144336
$[wxy]$	$S(wxy) - \bar{y}\,S(wx)$	98.208762 − 4.5966917(21.1690)	= .901395	1.120621
b	$\frac{[wxy]}{[wx^2]}$	$\frac{.901395}{.152738}$	= 5.901577	7.763974
$[wy^2]$	$S(wy^2) - \bar{y}\,S(wy)$	523.454590 − 4.5966917(112.71088)	= 5.357424	8.745435
χ^2	$[wy^2] - b[wxy]$	5.357424 − 5.901577(.901395)	= .037772	.044963

will fall within the sampling error as required for a valid assay. The equations in the following sections are based upon the assumption that this, in fact, is true. Chi-square not only tests this assumption critically but provides as well a useful check on the arithmetic of the whole computation, since mistakes often lead to excessively large or to impossible, negative values of χ^2.

The Measurement of Relative Potency.—Up to this point each individual curve has been computed separately and the explanation has been relatively brief, since a full description of the theory and computation is already in the literature (5). The individual results must be combined to obtain an expression of the most probable value of the potency of the unknown sample or experimental factor (as in the above example) relative to that of the standard; the calculation involved in these steps may be given in more detail. Gaddum (2) first proposed a formula for this expression, designating it as "M," and defining it as

$$M = \log \frac{\text{potency of first preparation (unknown)}}{\text{potency of second preparation (standard)}}$$

Thus M is the logarithm of the ratio of potencies. Remembering that potencies are inversely proportional to the doses producing equivalent biological effects, it may be seen that M has its simplest form when exactly equal effects have been obtained, in which case

M = weighted mean log-dose of standard − weighted mean log-dose of unknown = $\bar{x}_S - \bar{x}_U$, where the subscripts "S" and "U" refer, respectively, to the standard and the unknown sample, or may represent two variations in technique with the same material.

Corresponding to the weighted mean log-dosages, $\bar{x}_S$ and $\bar{x}_U$, the weighted mean effects in probits for standard and unknown may be designated as $\bar{y}_S$ and $\bar{y}_U$, respectively. In the above derivation of M it was assumed that the latter were equal, *i. e.*, that equal biological effects had been obtained. It seldom happens, however, that equivalent doses of two preparations produce exactly the same biological effect even if one has been fortunate enough to select exactly equivalent doses. When $\bar{y}_S$ is not equal to $\bar{y}_U$, a correction must be introduced for this inequality. It will be recognized that $\bar{y}_S - \bar{y}_U$ represents the difference in *effect* whereas M represents a difference in *log-dose*, so that to correct M for the difference in effect it is necessary to convert $\bar{y}_S - \bar{y}_U$ into units of log-dose.

The form of this conversion depends upon whether the two samples or experimental conditions are qualitatively similar, so that their respective dosage-effect curves do not differ significantly in slope. If the samples differ qualitatively and the dosage-effect curves are not parallel, the log-ratio of potencies, M, will depend upon the probit at which the two curves are compared. In this case some given level of effect, such as five probits (50 per cent effect), must be selected for purposes of comparison. Such comparisons will have, as a consequence, only limited validity

However, when the two curves have substantially the same slope, so that two parallel lines can be drawn through the two sets of points as shown by the broken lines in Fig. 1, comparisons of potency are valid at all levels of effect. The significance of any difference in slope may be tested by computing χ^2 for the difference, χ_b^2, which is given by the formula

$$\chi_b^2 = \frac{(b_S - b_U)^2}{\frac{1}{[wx^2]_S} + \frac{1}{[wx^2]_U}} \tag{1}$$

when the observed probits agree with their respective curves within the sampling error. When χ_b^2 exceeds 3.84, the dosage-effect curves for the two samples differ more than would be expected by chance and caution should be used in comparing them by M. If a lower value of χ_b^2 is obtained, it usually may be assumed that the samples are qualitatively similar and that the two parallel lines will represent a better estimate of the true slope than either line considered alone. This latter condition has been found in the great majority of the tests in this laboratory and is the only one considered below.

The common or combined slope, b_c, of the two parallel lines can be derived from terms already calculated as

$$b_c = \frac{S[wxy]}{S[wx^2]} \tag{2}$$

Since b_c, by definition, measures the change in probit effect associated with a unit change in log-dose, it follows that its reciprocal, $1/b_c = s_c$, gives the change in log-dose corresponding to one probit. This value, which has been termed λ by Gaddum (2), is the population standard deviation of the just effective log-dose and may be used in converting $\bar{y}_S - \bar{y}_U$ into log-dose units in arriving at the general form for M as

$$M = \bar{x}_S - \bar{x}_U - s_c(\bar{y}_S - \bar{y}_U) \tag{3}$$

where the sign of M is negative for samples less potent than the standard and positive for samples stronger than the standard.

One should not be satisfied with a mere statement of the most probable value of the potency of a sample but should require that its precision be known as well, so that the reliability of the assay can be judged. This information is furnished by computing the standard error of M, s_M, which is given with sufficient accuracy by the formula

$$s_M = s_c\sqrt{\frac{1}{S(w)_S} + \frac{1}{S(w)_U} + \frac{(\bar{y}_S - \bar{y}_U)^2 s_c}{S[wxy]}} \tag{4}$$

Like M, s_M is in logarithmic units of dosage so that the quantities $M + s_M$ and $M - s_M$ give the range within which M may be expected to fall in two out of three assays repeated under similar conditions. Few bioassayists are willing to be wrong as often as one-third of the time so that they usually adopt the more conservative range of $M \pm 2s_M$ which reduces the odds to less than one in twenty. It is worthy of note that the still more stringent limits of one in one hundred have been adopted for biological assays by the British Pharmacopœia (1936 Addendum) as indicated by the following quotation:

"ERRORS OF BIOLOGICAL ASSAYS. In expressing the limits of error of biological assays the term 'limits of error ($P = 0.99$)' is used. The statements of the errors of these assays are based on the convention that, for practical purposes, a probability of 0.99 is equivalent to certainty. In other words, it has been estimated that the result of the assay will be within the stated limits 99 times out of every 100 times that the assay is made. These limits are given as percentages of the true result. Thus, the statement 'limits of error ($P = 0.99$) 95 and 105 per cent.' means that it has been estimated that in 99 assays out of 100 the result will be greater than 95 per cent., and less than 105 per cent., of the true result.

"If the error of the test, or its logarithm, is normally distributed, the stated limits of error correspond to the range covered by ± 2.576 times the standard deviation."

Although in treating the data by this method all computations and statistical tests of significance are made in terms of logarithms, these are transformed to original units for final statements of relative potency. The most probable estimate of the relative potency of two samples or of a single sample when assayed by two different techniques is given by the antilogarithm of M,

which is multiplied by 100 if percentage potency is preferred. At odds of twenty-one in twenty-two this ratio is established within the limits given by the antilogarithm of $M + 2s_M$ and of $M - 2s_M$, or if the more stringent limits of ninety-nine in one hundred adopted by the British Pharmacopœia are preferred, s_M is multiplied by 2.576 instead of by 2. From the very nature of the logarithmic transformation, the upper limit in original units will differ more from the most probable value than will the lower limit. If the error is relatively small, the inequality may not be large and an approximate average error may be more useful as a descriptive term. As shown by Cochran (10), this is given by the formula

$$s.\ e.\ \text{of relative potency} = 2.3026\ s_M\ (\text{antilog. } M) \qquad (5)$$

The computation of the log-ratio of potencies and its error may be illustrated by substituting in the above equations the parameters of the numerical example listed in Table II. To determine whether the two dosage-effect curves differ significantly in slope, equation (1) is used to compute

$$\chi_b^2 = \frac{(5.902 - 7.764)^2}{\frac{1}{0.1527} + \frac{1}{0.1443}} = 0.256.$$

Since χ_b^2 is considerably less than 3.84, the two curves may be considered as parallel within the sampling error and their slopes may be combined by equation (2) to obtain

$$b_c = \frac{0.9014 + 1.1206}{0.15274 + 0.14434} = 6.8064 \text{ and } s_e = 0.14692.$$

This combined slope has been used in drawing the parallel, broken lines in Fig. 1, their positions being fixed by the means $\bar{x}_S$, $\bar{y}_S$ and $\bar{x}_U$, $\bar{y}_U$. The log-ratio of potencies may now be computed from equation (3) as

$$M = 0.86334 - 0.56303 - 0.14692\ (4.59669 - 4.72694) = 0.31945$$

in which, as in Table II, injection into the lymph sac has been considered as the "standard" and into the thigh muscles as the "unknown." Graphically, M may be represented as the horizontal distance between the two parallel lines in Fig. 1.

The standard error of the log-ratio of potencies is given by equation (4) as

$$s_M = 0.14692 \sqrt{\frac{1}{24.52} + \frac{1}{23.95} + \frac{(4.59669 - 4.72694)^2\ 0.14692}{2.0220}} = \pm 0.04253.$$

If, under these conditions, digitalis had the same potency by both routes of injection, M would not differ significantly from 0 (which corresponds to 100 per cent) *i. e.*, M would be less than twice its standard error. In the present case, however, the ratio of M/s_M exceeds 2 considerably so that there is much less than one chance in twenty that the potency was identical under both experimental procedures. In original units, the ratio of the intramuscular potency to the lymph sac potency was equal to the antilogarithm of 0.31945 or to 2.087, *i. e.*, to 208.7 per cent. The approximate standard error of the result, which corresponds to odds of two in three, was determined by means of equation (5) as $\pm 2.3026\ (0.04253)\ (208.7) = \pm 20.4$ per cent. At odds corresponding to twice the standard error the observation was established within the limits of 171.5 and 253.8 per cent. Despite the statistical significance of the result of this single comparison, it was desirable to reduce the error to narrower limits by replication (see Table IV). The general aspects of reducing the standard error are discussed in the next section.

METHODS FOR INCREASING THE PRECISION OF M.

The final objective of a bioassay is to determine M with a known level of precision as indicated by s_M. It is often impossible to obtain the desired precision with a single assay, and even when it is possible, one might prefer to continue an experiment over several independent component tests to broaden the basis for his conclusions. Methods for increasing precision, therefore, are of several types. One is to attain the smallest error in each individual assay by following an efficient design. Another is to draw upon the relevant experience of other assays through the medium of a standard curve. A third and most important method is to combine the evidence

from several assays to obtain a mean M with a reduced error. These and related problems may be considered next.

The reduction of s_M by the Design of the Individual Assay.—Since the result of an assay is measured in terms of M, it follows that the smaller the standard error of M, s_M, the greater is its reliability. A study of the various components in the equation for s_M indicates how to plan assays so as to minimize this error. Two possibilities are open to the experimenter. The first and more obvious technique is to increase the number of animals used in a given test. Since w, the weight assigned to each observation, is proportional to the number of animals upon which it is based and since w occurs in the denominator of each fraction in equation (4), s_M decreases proportionately to the increase in the square root of the number of individuals. Thus the addition of ten frogs on each dose will effect a proportionately greater reduction in s_M if the original number is ten than if it is twenty, and soon a limit is reached where other methods of increasing precision become more profitable. In general, it is better not to enlarge a single test beyond the point where the frogs can be handled easily but rather to repeat the assay several times independently.

The second possibility is to plan the experiment so as to make the most efficient use of each animal, a problem which may be approached from several angles. The information in a given probit effect and hence its weight, w, depends not only upon the number of animals but also upon a weighting coefficient determined from the probit expected at each dose. Since the weighting coefficient is largest at an expected probit of five (50 per cent effect) and diminishes both above and below this point, $S(w)_S$ and $S(w)_U$ decrease as the dosage interval is enlarged. The use of too small a dosage interval, on the other hand, is objectionable because it may so reduce $S[wxy]$ that the third term under the square root contributes unduly to the error. A narrower interval also reduces the reliability of s_e. With either two or three doses in a dosage-effect curve, these two opposing tendencies are balanced most satisfactorily when the expected effects of the high and low doses are from 0.9 to 1.0 probit above and below 5. Assuming that it is somewhat impractical to use more than three doses of each preparation in a given assay, the only choice lies between a two or three-dose technique if individual dosage-effect curves are desired. With forty frogs available for each preparation, an assay in which twenty frogs are used on each of two doses may be expected to have an average s_M slightly larger than if the forty frogs were distributed between three doses with fifteen, ten and fifteen frogs on the low, intermediate and high doses, respectively. The three-dose arrangement would be preferred, therefore, quite apart from other advantages discussed later.

The precision of an assay as measured by s_M is also dependent upon the difference in the mean probits for the two curves, $\bar{y}_S - \bar{y}_U$. When the potency of the unknown has been estimated from preliminary experiments and the test planned so that $\bar{y}_U$ differs from $\bar{y}_S$ only by chance variation in sampling, the component in equation (4) containing $(\bar{y}_S - \bar{y}_U)$ frequently averages less than 2 per cent of the total of the three terms beneath the radical or square root sign. But if the two samples differ significantly in the effects they produce, this component can contribute heavily to the error. For this reason alone, an assay in which there is a wide gap between the assumed and the observed potency of the unknown is never as precise as when the experiment confirms the assumption. When an assay is repeated, therefore, the assumption for each successive trial should be the combined value of M from all earlier tests so as to reduce $\bar{y}_S - \bar{y}_U$ to within the sampling error.

A third factor in s_M is the reciprocal of the slope, s_e. Since s_M is directly proportional to s_e, the steeper the slope the more precise the assay. If dosages are selected which give the most efficient levels of effect as described above, the terms beneath the radical sign are independent of the slope. Then the steeper the slope the smaller is the standard error of the assay even though the reliability of the estimate of the slope diminishes. When an experiment is planned specifically for a comparison of slopes, the most efficient procedure is to use only two dosage levels, spaced so that they give 7–10 and 90–93 per cent of positive effects.

The Question of a Standard Curve.—It will be noted that the above design does not depend upon a standard curve but that the slope of such a curve is determined independently in each assay. If forty frogs are used on the standard and forty on the unknown—equal numbers on each preparation being the most efficient allocation of a given amount of experimental material—the combined slope has a standard error not less than 20 per cent of its observed value. It may be contended that a standard curve, such as is used by many bioassayists, avoids this error since

it is based upon a large number of animals and in consequence has a high reliability. This would be true, however, only if it were known that the predetermined slope of the standard curve were applicable to the assay in question, a fact which can be determined with certainty only by obtaining the slope under the conditions of the assay and comparing it with that of the standard curve. The slope of the dosage-effect curve may vary between laboratories and with the season. Until considerably more is known about the variations in the dosage-effect relation, assays should be planned so that they are self-contained and not dependent upon an assumed slope.

The practice of employing more than one dose in each assay has the advantage, moreover, that the data on the standard from separate assays can always be combined, either currently or subsequently, if statistical test shows that the individual determinations are, in fact, parallel. In this way one can arrive at an improved estimate of the slope of the characteristic dosage-effect curve for the standard and if experience demonstrates its advisability, a "standard curve" can be built up eventually which will have a much broader basis than if established as the result of an isolated series of tests. The combined slope of such a curve may be computed from equation (2) which may be used to combine the data from any number of assays having parallel dosage-effect curves. To determine whether they are sufficiently parallel to justify combination the following chi-square test may be applied:

$$\chi_b^2 = S\{[wx^2]_1 (b_1 - b_c)^2\} \qquad (6)$$

where subscript "1" refers to each individual result. Hence, whenever a "standard curve" would be valid, this procedure is always available for increasing the precision of M and s_M.

Combining the Results of Replicated Assays.—Although no single assay may suffice, the log-ratio of potencies can be determined to any reasonable level of precision by sufficient replication. The results of independent assays seldom have identical standard errors and therefore are not of equal value, so that in combining such results each should be given a weight proportional to the information it contains. The information in a parameter has been shown by Fisher to equal the reciprocal of its variance, a principle which has been used in weighting the individual observations when computing the dosage-effect curve for any given assay. In the present case the information in each assay as a whole is equal to $1/(s_M)^2$, which is used as a weight in computing the weighted mean as

$$\overline{M} = \frac{S(w_M M)}{S(w_M)} \qquad (7)$$

where $w_M = 1/(s_M)^2$. This equation is identical in principle and in form with those for computing the weighted mean log-dose ($\bar{x}$) or weighted mean probit ($\bar{y}$) (Table II).

All of the individual M values combined in a mean log-ratio of potencies should agree with one another within their sampling errors, especially when assaying an unknown sample of digitalis. χ^2 can be used to test whether the separate estimates of M are mutually consistent by an equation analogous to that used for χ^2 in Table II, namely,

$$\chi_M^2 = S(w_M M^2) - \overline{M}S(w_M M) \qquad (8)$$

which will have one less degree of freedom than the number of independent values of M entering into the equation. If all determinations are homogeneous within the limits of χ_M^2 or an equivalent test, the standard error of the mean $\overline{M}$ is given by the equation

$$s_{\overline{M}} = \sqrt{\frac{1}{S(w_M)}} \qquad (9)$$

But if χ_M^2 indicates a significant degree of heterogeneity, as sometimes occurs, the standard error given in equation (9) must be increased to include the variation between the component M's, so that then

$$s_{\overline{M}} = \sqrt{\frac{\chi_M^2}{(N-1)S(w_M)}}, \qquad (10)$$

where N is the number of individual M's entering into the mean.

CRITERIA FOR SELECTING AN ASSAY TECHNIQUE.

Having in mind the quantitative basis for the all-or-none assay, we may now consider which criteria show the greatest promise for discriminating between alternate techniques. Of the several parameters described above, four suffice to characterize the assay procedure.

The first of these is the chi-square test given as the last item in Table II. It is used here to determine whether the points on the plot of probit *vs.* log-dose diverge so far from linearity that it is inadvisable to fit them with a straight line. Since it is possible to draw only one straight line through two points, at least three doses must be used before there can be any divergence which is measurable by χ^2 and the fact that otherwise χ^2 cannot be computed is another reason for distributing the number of available frogs over three or more doses. In cases where χ^2 indicates a divergence from linearity, the whole experimental procedure should be scrutinized searchingly for possible causes of heterogeneity, such as a change in the source and storage conditions of the frogs, failure to assign the frogs at random to the different dosages, unequal exposure to some influence during the assay, etc. Thus χ^2 is a measure of the homogeneity of the frogs between dosages and of the experimental conditions. A procedure for which the chi-square test continues to indicate heterogeneity despite all possible precautions should be viewed unfavorably in comparison with alternatives which yield more homogeneous data under similar conditions. Thus the first criterion for a good assay procedure is a value for χ^2 which is consistently within the error of sampling.

The second parameter characterizing any assay is b, the slope of the dosage-effect curve. As a measure of the change in effect per unit change in log-dose, it is evident that any assay technique yielding a high value for b deserves consideration. Burn (11) has also emphasized this point. The fact that different laboratories have reported different slopes shows that the slope can be increased experimentally and any such change in technique would lead to an immediate improvement in precision. In searching for a procedure giving a steep dosage-effect relation, the constancy of a given slope from one assay to the next must not be overlooked. This can be checked by computing χ_b^2 as given by equation (1) or (6) and by relating the variation in b to other factors in the experiment. The second criterion suggested for a good assay technique is a consistent and relatively high value for b.

The third characteristic by which procedure is to be judged is the magnitude of s_M, the standard error of the log-ratio of potencies for an individual assay as given by equation (4). Although partly a corollary of the second criterion, the most precise method is clearly that which yields the lowest value of s_M. For this factor to have its full diagnostic value, assays should be designed with the precautions discussed in an earlier section on the reduction of s_M. A consistently low value of s_M is then a suitable third criterion for a good assay technique.

The fourth requirement is that the procedure shall give reproducible results. When an assay is replicated, the successive values of M should agree with one another within the sampling error, as measured by χ_M^2 computed from equation (8) or its equivalent. In principle this is by no means a new criterion since it has served as the acid test for recommending many procedures in the past. One of the more important advantages of the present quantitative approach is that it provides unequivocal, objective standards for judging whether or not successive assays are in agreement.

In proposing these criteria, it is anticipated that they will find their greatest usefulness in evaluating the results of research. No doubt many will find that the increased objectivity and efficiency attending these modes of analysis will more than repay the time invested in designing their experiments and in computing their results. In no sense can the criteria be substituted for accurate and well-planned experimentation, without which they are of little use. Nor can they be expected to resolve unaided all difficulties in selecting the best method for the bioassay of digitalis with frogs, if only because of two important elements which are not weighed by the proposed criteria, namely, practicability and experimental objectivity. It goes without saying that these factors will be conclusive in choosing between two procedures which appear equally advantageous in the light of the tests proposed above.

COMPARISONS OF PROCEDURE BASED UPON THE PROPOSED CRITERIA.

Of the several modifications of procedure which are being investigated and weighed in the light of the proposed criteria, two have reached a stage where a report may be justified.

Experimental Procedure.—All of the tests followed the same general plan. As a rule, two factors involving four dosage-effect curves were compared in each experiment, all other factors being kept as uniform as possible. Three dosage levels were used in each experiment with fifteen to twenty frogs on each dose.

The frogs came from two sources. In tests conducted prior to May 1939, they were from Vermont, having been stored there on a lake bottom since November 1938, and shipped to the laboratory as needed in four-gross lots. Later tests were made on frogs shipped in similar lots from a dealer in Wisconsin. Upon arrival, the frogs were segregated as to sex and in some cases the males were divided as to weight into light and heavy groups, prior to storage in running water at a temperature below 15° C. It was not possible, because of limited facilities, to store the frogs for a uniform period prior to transfer to the assay tank on the afternoon of the day before the test. The frogs were kept singly as far as possible, especially during over night assays.

The preparation of tinctures from standard digitalis powders followed the U. S. P. XI method uniformly using 1 Gm. of powder for each 10 cc. of menstruum in cases where direct comparisons of two or more powders were involved. The mixture of powder and menstruum was shaken mechanically and intermittently for twenty minutes in every hour during the 24-hour maceration period.

In the preparation and injection of the test dilutions of the tinctures, every effort was made to obtain uniformity with respect to the relative volume of the fluid injected and its alcoholic content, unless these factors were varied experimentally. Except in special cases, the test dilutions of digitalis contained about 23 per cent alcohol. This represents about the maximum content that allows a margin of safety below the U. S. P. XI limit of 25 per cent. Furthermore, it can be obtained with a minimum of manipulation, since it is the average alcoholic content resulting from a 1:3 dilution with water of U. S. P. XI Tincture of Digitalis (67 to 72 per cent by volume of C_2H_5OH).[1]

Not infrequently it was necessary to dilute less than 1:3 since the volume of the injected fluid per Gm. of frog was kept the same for all three doses of each test. In such cases some of the alcohol was removed by evaporation in order to keep the final alcoholic content at 23 per cent. Data have been taken in this laboratory which make it possible to predict the amount of evaporation under an air stream needed to reduce the amount of alcohol sufficiently to yield a test dilution containing almost any desired alcoholic content. It is probably not generally recognized how difficult is the matter of removing all or even a large part of the alcohol from a tincture residue. For example, in the test of June 19 (Table III) it was desired to use a test dilution containing 5 per cent alcohol in a volume of 0.01 cc. per Gm. of frog. To fulfil these requirements for the highest dose needed in the one-hour method (0.0063 cc. per Gm. of U. S. P. XI Standard Preparation of Digitalis) it was necessary to evaporate off 70 per cent of the original weight of a measured sample of the tincture. The alcoholic content actually attained, as determined on a subdivision, was 4.7 per cent.

In each experiment a separate dilution was prepared for each dosage level, using an appropriate amount of tincture and adding or removing alcohol as required so that the final test dilutions contained the desired doses in either 0.01 or 0.02 cc. of fluids with the desired alcoholic contents. With a view toward convenience in the computations, the doses selected were such that their logarithms were round numbers, uniformly spaced. The interval between doses for the one-hour method was usually 0.10 log and for the over night method, 0.05 log. All the doses used in any experiment were assigned at random to the frogs (in groups of five) by shaking numbered tags, so that all groups had an equal chance of receiving each dose of each test preparation.

In reading the results of the one- and four-hour test, a rigid interpretation of the U. S. P. XI definition was adopted, namely, ventricle in systolic standstill upon exposure, or going into standstill upon gentle mechanical stimulation; auricles widely dilated and *in standstill*. In reading the results of the over night or lethal dose method, there was virtually no room for the exercise of personal judgment. Rarely does one encounter a frog which is not unquestionably dead or alive 16 to 24 hours after injection.

[1] In this connection it should be noted that the official Standard Preparation of Digitalis (U. S. P. XI, p. 397) when prepared as directed using a menstruum of 4 parts by volume of alcohol and 1 part of distilled water, contains about 74 per cent alcohol and in this respect differs from U. S. P. XI Tincture of Digitalis.

The Influence of Alcohol on the Apparent Potency.—In view of the results reported by Rowe (12) considerable attention was devoted to the possible influence of the alcoholic content of the injection fluid upon the apparent potency of the same sample of digitalis. Toward this end, eight comparisons were made between test dilutions of digitalis containing approximately 5 and 23 per cent alcohol, respectively, each comparison involving the use of ninety to one hundred twenty frogs. As may be noted from the summary of the data in Table III, three standard digitalis powders were used as test material in these comparisons under the wide variety of conditions indicated in columns 2, 3 and 5.

TABLE III.—INFLUENCE OF ALCOHOL CONTENT OF TEST DILUTION ON POTENCY.

(1) Date 1939.	(2) Route.	(3) Time.	(4) Material.	(5) Volume.	(6) $M \pm s_M$.	(7) $(b_5 - b_{23}) \pm$ s. e. diff.	(8) $b_c \pm$ s. e. b_c.	(9) χ^2 23 Per Cent.	(10) χ^2 5 Per Cent.
4/18	*L*	1h	U. S. P.	.02	−.0151 ± .0668	1.739 ± 2.941	3.996 ± 1.468	.692	1.225
4/18	*L*	1h	1936	.02	−.0081 ± .0471	4.264 ± 3.076	5.514 ± 1.534	.069	.000
4/20	*L*	1h	U. S. P.	.02	.0108 ± .0447	2.131 ± 3.504	6.236 ± 1.750	1.650	.124
4/20	*L*	1h	1926	.02	−.0350 ± .0536	3.951 ± 3.449	5.218 ± 1.719	.727	.120
6/19	*M*	ON	U. S. P.	.01	.0327 ± .0170	−9.039 ± 8.097	18.073 ± 3.946	1.672	.220
6/19	*M*	1h	U. S. P.	.01	−.0174 ± .0423	−3.912 ± 3.184	6.217 ± 1.573	1.279	.589
6/24	*M*	ON	U. S. P.	.01	.0244 ± .0254	− .050 ± 6.654	10.824 ± 3.321	1.811	.000
6/24	*M*[1]	ON	U. S. P.	.01	−.0085 ± .0230	1.618 ± 6.281	10.966 ± 3.140	1.309	1.994
Weighted Mean	$\overline{M}$ =				+.0131 ± .0107	1.227 ± 1.350			

Conclude: Potency with 5 per cent alcohol = 103.1 ± 2.5 per cent of that with 23 per cent alcohol.
In determining M and the difference in respective slopes, the preparation of 23 per cent alcohol content was taken as the standard. Thus, in column 7, $(b_5 - b_{23})$ indicates the difference in the slopes obtained, respectively, by the use of 5 and 23 per cent alcohol contents. Also tabulated is the standard of errors of the difference in slopes.

[1] Female frogs used; all others were male frogs.

The value of M and s_M for each comparison is listed in column 6. In only one case (6/19, over night method) did M exceed its standard error, s_M, and then not significantly, so that it was unnecessary to compute χ_M^2 to test the agreement of values of M prior to combining them. The weighted mean of the series, $\overline{M}$, and its standard error were 0.0131 ± 0.0107. In terms of percentages, this result indicates that the same digitalis sample when injected with 5 per cent alcohol exhibited a potency 103.0 ± 2.54 per cent of that exhibited when injected with 23 per cent alcohol. Thus under the conditions of our experiments, a fourfold change in the alcoholic concentration did not alter the outcome of the assay significantly. The experimental error of this series was sufficiently low, as indicated by its standard error, that an $\overline{M}$ corresponding to less than 93.8 or more than 106.6 per cent would have pointed to a highly significant influence ($P = 0.99$) of the alcoholic content of the test dilutions upon the estimated relative potency. No one test had a precision within these limits but because the individual values from assays on more than 720 frogs were all in agreement, they could be combined so that the error of the final estimate was reduced to one-third of that observed in some of the individual assays.

The influence of variation in alcoholic content upon the slope of the dosage-effect curve may be judged from the data listed in column 7, which show the difference in slope and the standard error of the difference for each comparison. In no experiment was the difference significantly greater than its standard error. The trend of the data is in the direction of a steeper dosage-effect curve with the use of 5 per cent alcohol, particularly for lymph sac injections, and with sufficient replication of suitably designed experiments, this trend might prove to be significant. Any advantage found, however, would have to be considerable to outweigh the inconvenience of evaporating off the alcohol to such a low concentration.

Column 8 lists for each comparison the value of b_c and its standard error, the significance of which will be discussed in the following section.

In columns 9 and 10 are listed the respective values of χ^2 for the two percentages of alcohol tested. Although none of the values indicates any noteworthy degree of heterogeneity, so that both techniques would be considered equally valid, it is evident that the χ^2 is generally lower in the series with the 5 per cent alcohol. In two experiments of this series, the χ^2 was zero since all three of the observed points fell exactly on a straight line. Any further significance of these comparative values of χ^2 cannot be evaluated at present but remains a subject for further investigation.

The Influence of Route of Administration upon Absorption.—As indicated in the numerical example given above, two routes of administration of digitalis have been tested in our survey of the

TABLE IV.—COMPARISON OF INTRAMUSCULAR AND LYMPH SAC INJECTION.

(1) Date 1939.	(2) Time.	(3) Volume Cc./Gm.	(4) Material.	(5) $M \pm sM$.[4]	(6) $(b_m - b_l) \pm$ s. e. diff.	(7) $b_g \pm$ s. e. b_g.	(8) χ^2 Muscle	(9) χ^2 Lymph
5/24	1h	1	U. S. P.	.3194 ± .0425	1.862 ± 3.671	6.806 ± 1.835	.045	.038
6/30	1h	.02	U. S. P.	.2421 ± .0482	.694 ± 3.523	5.975 ± 1.761	.087	.597
7/11	1h	.02	U. S. P.	.3207 ± .0463	− .226 ± 3.526	6.431 ± 1.763	.089	.676
Weighted Mean	1h		U. S. P.	.2969 ± .0283	.748 ± 2.062			
5/25	1h	[1]	1936	.0775 ± .0533	−1.729 ± 3.165	5.188 ± 1.549	.112	.043
7/11	1h	.02	1936	.2387 ± .0478	1.048 ± 3.455	5.779 ± 1.727	.087	.001
Weighted Mean	1h		1936	.1608 ± .0356	− .462 ± 2.333			
6/12	ON[2]	.01	U. S. P.	.0486 ± .0214	3.761 ± 6.848	12.977 ± 3.422	.393	.009
6/12	ON[3]	.01	U. S. P.	.0108 ± .0157	−3.880 ± 6.411	16.870 ± 3.199	1.538	.897
6/22	ON	.01	U. S. P.	.0261 ± .0160	1.029 ± 6.835	16.663 ± 3.412	2.936	.465
6/22	ON	.02	U. S. P.	.0725 ± .0356	5.007 ± 6.389	9.366 ± 3.194	.080	.008
6/30	ON	.02	U. S. P.	.0107 ± .0424	−6.522 ± 7.172	6.963 ± 3.574	.239	.262
Weighted Mean	ON		U. S. P.	.0274 ± .0093	.034 ± 3.000			

Conclude: U. S. P. (one-hour): Potency of Intramuscular = 198.1 ± 12.0 per cent of lymph sac.
International 1936 (one-hour): " " = 146.8 ± 12.0 " " " "
U. S. P. (over night): " " = 106.5 ± 2.3 " " " "

Male frogs were used on all experiments except on 6/30/39 when all females were used. Alcohol content of injected material approximately 23% in all experiments.

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[1] Volume of injected material was confounded with route of injection, *i.e.*, 0.01 cc./Gm. given intramuscularly and 0.02 cc./Gm. given by lymph sac.

[2] Light-weight frogs used (average 19.4 Gm.).

[3] Heavy frogs used (average 27.2 Gm.).

[4] In determining M and the difference in respective slopes, results of lymph sac injection were taken as standard. Thus, in column 6 ($b_m - b_l$) indicates the difference in the slopes obtained, respectively, by the intramuscular and lymph sac injections; also tabulated is the standard error of the difference in slopes.

factors which may influence assay results with frogs. The report of Dooley and Higley (6) suggested that the intramuscular route was worthy of an early trial. In Table IV the data are summarized from ten comparisons of intramuscular with lymph sac injection. These were made with both the one-hour and the over night methods (column 2) and two comparisons were made with the four-hour method, these data not being included because of their incompleteness. Both the U. S. P. XI Reference Digitalis Powder and the 1936 International Standard Powder were used (column 4). The volume of the injected fluid is recorded in column 3 and, as noted, volume was confounded with route on May 24 and 25. It is clear from the data in column 5 that the influence of route on the potency was determined largely by the length of time the digitalis was allowed to act. The two powders also seemed to differ significantly in this respect, so that the data obtained by the one-hour method have been combined separately for each powder.

From the combined results of three assays by the one-hour method, it is seen that the U. S. P. XI Reference Digitalis Powder had twice as great a potency when injected intramuscularly as when injected into the lymph sac. It may be inferred, therefore, that in one hour not more than one-half of the active glucosides of the powder were absorbed effectively from the lymph sac as compared with the amount absorbed following intramuscular injection. Similarly it may be inferred that only about two-thirds of the activity of the 1936 International Standard Powder was absorbed effectively from the lymph sac in one hour. The limited data available indicate that the observed difference in the two standards is probably significant. Further work is now in progress to establish this point.

The results of the five assays on the U. S. P. XI Reference Digitalis Powder by the over night method agreed among themselves within the sampling error ($\chi_M^2 = 3.87$ with 4 degrees of freedom). Their combined value, $\overline{M} = 0.0274 \pm 0.0093$, demonstrates that more complete absorption was apparently obtained following intramuscular injection even with the longer period of observation. Although the difference in potency was small, 106.5 ± 2.3 per cent, the ratio of $\overline{M}$ to its standard error was $0.0274/0.0093 = 2.95$. Thus these tests on about 500 frogs show that by the over night method the potency of this digitalis powder was slightly but significantly ($P = 0.99$) greater by the intramuscular route than *via* the lymph sac.

The differences in slope and their standard errors are listed in column 6. From this point of view it is obvious that both routes of administration were equal. The standard errors of the differences in slope were much larger with the over night technique than with the one-hour method, due to the use of smaller interval between doses for the over night method necessitated by its steeper slope (0.05 log as against 0.1 log for the one-hour). Column 7 lists the combined slope, b_c, and its standard error for each assay. Examination of these data and those of column 8, Table III, reveals that the dosage-effect curve was much steeper for the over night method than for the one-hour assay. This finding is not in agreement with the result reported by Edmunds, Moyer and Shaw (13), who concluded from experiments with the lymph sac method of injection "that regardless of the period of observation (one-hour or lethal dose) . . . the characteristic curve for digitalis has the same slope." Without the data underlying the above quotation, this discrepancy cannot be examined further, but in the experiments at this laboratory the steeper slope of the over night curve is the outstanding feature of data on comparisons of the methods embodying the two periods of observation. It is this steeper slope that accounts for the greater precision of the estimate of potency obtained by the over night method, as shown by s_M in Table IV. Thus application of the second criterion proposed above reveals a decided advantage in favor of the over night method.

Scrutiny of the respective chi-square values for the two routes of injection reveals no significant difference. With one exception (over night assay of 6/22 with 0.01 cc. volume) the chi-squares did not approach a value which would indicate a significant degree of heterogeneity.

SUMMARY.

1. Further improvement in the digitalis assay on frogs can be facilitated by objective criteria for testing the effectiveness of any proposed modification of procedure. Due to the nature of the assay, such criteria are necessarily statistical in character and in a well-designed experiment can be computed from the data of a self-contained assay. By transformation of dosages to logarithms and of percentage

effect to probits, the sigmoid dosage-response curves for the two materials or procedures involved in the test are fitted by parallel straight lines. Then the horizontal distance between them measures with a calculable precision the log-ratio of their potencies, $M \pm s_M$. The computation of these and related parameters is illustrated with a numerical example.

2. Methods are described for increasing the precision of M by an efficient design of the individual assay, by utilizing past experience relative to the slope of the standard curve where applicable and by combining the results of replicated assays to obtain a more precise weighted mean log-ratio of potencies.

3. On the above statistical basis, four criteria are proposed for evaluating an assay procedure: (*a*) a value of chi-square which indicates that the several groups of frogs used in the test were homogeneous and comparable, (*b*) a consistent and relatively steep slope of the parallel dosage-effect curves, (*c*) a consistently low value of the standard error of the log-ratio of potencies, s_M, and (*d*) agreement of replicated determinations of M within the sampling error. In conjunction with a knowledge of the practicability and experimental objectivity of a procedure, these criteria should be conclusive in the development of an improved technique.

4. These criteria have been applied in a comparison of the effects produced by injection of the same sample of digitalis in test dilutions containing 5 and 23 per cent of alcohol. The apparent potencies of the U. S. P. XI Reference Digitalis Powder and of the International 1926 and 1936 Standard Digitalis Powders were not influenced by this fourfold change in the alcoholic content of the injected test dilutions, the same digitalis powder when injected with 5 per cent alcohol exhibiting a potency 103.0 ± 2.54 per cent of that exhibited when injected with 23 per cent alcohol.

5. The relative effectiveness of digitalis injected intramuscularly has been compared with that injected in the lymph sac. One hour after injection the effective absorption of U. S. P. XI Reference Digitalis Powder from the lymph sac was about one-half that from the thigh muscles and even over night the potency of digitalis was slightly but significantly greater (106.5 ± 2.3 per cent) by the intramuscular route than *via* the lymph sac. The difference was less pronounced with the 1936 International Standard Powder. The over night assays showed a smaller standard error than the one-hour tests because of a consistently steeper dosage-effect curve.

REFERENCES.

(1) Trevan, J. W., *Proc. Roy. Soc., B*, 101, 483 (1927).
(2) Gaddum, J. H., *Med. Res. Council, Special Report Series*, No. 183 (1933).
(3) Bliss, C. I., *Science*, LXXIX, 409 (1934).
(4) Bliss, C. I., *Ann. Appl. Biol.*, 22, 307 (1935).
(5) Bliss, C. I., *Quart. J. Pharm. Pharmacol.*, 11, 192 (1938).
(6) Dooley, M. S., and Higley, C. D., JOUR. A. PH. A., 11, 911 (1922).
(7) Fisher, R. A., and Yates, M. A., "Statistical Tables for Biological, Agricultural & Medical Research," Oliver & Boyd, London (1938), Table IX.
(8) Fisher, R. A., and Yates, M. A., *Ibid.*, Table XI.
(9) Fisher, R. A., and Yates, M. A., *Ibid.*, Table IV.
(10) Cochran, W. G., *Ann. Appl. Biol.*, 25, 426 (1938).
(11) Burn, J. H., "Biological Standardization," Oxford Univ. Press (1937).
(12) Rowe, L. W., JOUR. A. PH. A., 27, 844 (1938).
(13) Edmunds, C. W., Moyer, C. A., and Shaw, J. R., *Ibid.*, 26, 290 (1937).

A COMPARATIVE STUDY OF TANNIC ACID, U. S. P.*[1]

BY CLIFTON E. MILLER[2] AND L. W. RISING.[3]

This investigation was initiated with a survey of the prior work done by others on the chemistry of tannic acid in the hope of finding the best method of developing an assay procedure. The published records of Mitchel (1) and Forbes (2) are typical of these previous studies. It seemed mandatory after careful scrutiny of the work of Mitchel and Forbes that a general study of tannic acid be made in order to determine the logical method of developing an assay for tannic acid. This paper describes that portion of the work.

Eleven samples of U. S. P. Fluffy Tannic Acid were obtained and used for this investigation. The tests for purity as outlined by the Pharmacopœia yielded results which were not congruent with the anticipated values. The amount of moisture was found to vary from 4.50 to 9.52 per cent and the ash from 0.01 to 0.16 per cent. A number of the samples gave positive tests for gums, dextrins and resinous substances.

The acetylation of tannic acid was attempted, using a mixture of tannic acid, acetic anhydride and pyridine. This mixture was placed in a shaking machine for two hours, and allowed to stand at room temperature for three days. The resulting yellowish-brown liquid was poured into ice water and the acetylated tannic acid liberated by the addition of dilute sulfuric acid. A grayish-white powder was obtained which, upon fractional crystallization, did not give a product of any definite purity as evidenced by the formation of resinous masses and in several cases products which melted from 118° C. to 135° C. We concluded, therefore, that if the above method be taken as typical of those available, the acetylation of tannic acid does not yield a definite compound.

In order to obtain some idea of the comparative values of the different tannic acids in terms of gallotannin, they were analyzed using the Lowenthal Method as modified by the A. O. A. C. (3). This method involves permanganate titration and gelatin precipitation. From the calculated results it was quite evident that the samples are not of the same purity and the non-tannin portion as found by the gelatin precipitation is high. A possible explanation of this variation of the non-tannin portion is that such factors as strength of solution, rate of filtration and time of shaking influence the precipitation of the tannins.

The determination of the melting point, effect of heat, hydrolysis with acids and fusion of tannic acid with alkalies gave results which suggest that tannic acid has an indefinite composition. The determination of various physical constants such as refractive index, surface tension, optical activity, titratable acidity, spectroscopic analysis were made with the idea perhaps that an assay might be developed from one of them but disappointing results were obtained.

Nierenstein's (4) results on the effect of various color reagents with tannic acid were confirmed and further elaborated in making a systematic comparison of the tannic acid with seventy-two color reagents. As this work progressed it became apparent that one of the major difficulties encountered in assays making use of color reactions was the inability to accurately estimate the slight variation in color between the various samples with any given color reagent.

In attempting to obviate this difficulty, a photoelectric colorimetric comparison was made of freshly prepared aqueous solutions of tannic acid from one-tenth of one per cent to one per cent in concentration. These solutions were prepared from stock solutions by diluting aliquots with distilled water to make the required concentrations. All readings were made at 25° C. A number 7-089 Fisher Electrophotometer was used in this investigation. A 125-mm. cell was used for

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[1] Abstracted from a thesis submitted to the Graduate School of the University of Washington by Clifton E. Miller, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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all samples. The variance for each sample over the range of concentration used and the variable reduction units demonstrate that colorimetric assays of tannic acid cannot be accomplished due to the inconsistency of the sample and difference in color. The numerical results are given in the following table.

TABLE I.—RANGE ONE. CONCENTRATION IN PER CENT.

Sample.	0.1.	0.2.	0.3.	0.4.	0.5.	0.6.	0.7.	0.8.	0.9.	1.0.
1	4.50	11.00	18.75	21.25	25.25	29.25	32.75	35.75	38.75	41.25
2	3.25	4.25	7.75	9.25	11.50	12.75	15.00	16.00	18.25	19.50
3	2.50	7.00	10.25	12.25	15.25	17.75	20.75	22.00	25.00	26.75
4	6.25	11.25	15.50	19.25	23.00	27.00	29.75	33.00	34.50	37.25
5	3.75	6.00	8.00	10.75	15.00	15.25	18.00	19.50	21.50	23.00
6	7.75	14.25	20.00	25.00	29.50	33.00	36.50	39.75	42.50	45.50
7	6.25	11.00	15.25	18.25	21.50	25.25	28.25	31.00	33.75	35.75
8	4.75	7.00	9.25	11.00	13.50	16.25	17.50	19.75	21.50	23.25
9	4.25	7.00	10.00	12.75	15.00	17.00	19.00	21.75	23.25	25.25
10	7.50	10.25	12.75	15.00	17.25	19.00	21.25	22.75	25.25	27.00
11	9.75	13.50	19.00	23.75	28.25	32.00	34.25	37.25	40.25	42.75

CONCLUSIONS.

1. The available samples of U. S. P. Fluffy Tannic Acid were purchased and compared by the tests for purity as outlined by the Pharmacopœia. The wide variation in these results gave proof of the variable composition of Tannic Acid Fluffy, U. S. P.

2. The determination of the melting point, refractive index, surface tension, optical activity, titratable acidity and spectroscopic analysis have been made with the hope that an assay might be developed making use of one of these constants.

3. A critical study of the various color reactions of tannic acid has been made together with an electrophotometric analysis, and as a result we conclude that an assay making use of color reactions is at present impractical.

BIBLIOGRAPHY.

(1) Mitchel, C. A., *Analyst*, 48, 2 (1923).
(2) Forbes, W. A., *Pharmaceutical Journal*, 116, 225 (1926).
(3) A. O. A. C., Washington, D. C., 4th Edition, page 196 (1935).
(4) Nierenstein, M., "Allen Commercial Organic Analysis," 5, 62 (1927).

THE VOLATILE OIL OF POLIOMINTHA INCANA.*

BY A. F. SIEVERS[1] AND C. G. MARSHALL.[2]

Among the species of southwestern plants under cultivation and observation at the Nursery of the Soil Conservation Service of the U. S. Department of Agriculture at Tucson, Arizona, one of particular interest to the senior writer while visiting the nursery in May 1938 was *Poliomintha incana* (Torr.), A. Gray (*Hedeoma incana* Torr.), N. O. *Labiatæ*. The one-and-a-half acre plot of this species was in full bloom and the strong odor of the foliage and flowers suggested the advisability of making a preliminary study of the volatile oil, inasmuch as a search of the litera-

* Presented before the Scientific Section, A. PH. A., Atlanta meeting, 1939.

[1] Bureau of Plant Industry, Dept. of Agriculture, Washington, D. C.
[2] Soil Conservation Service, Dept. of Agriculture, Washington, D. C.

ture failed to reveal any references to its previous examination. Accordingly, 165 pounds of the herb was cut on May 12th from 0.14 acre and after drying was shipped to Washington, D. C., where it was distilled. The 53 pounds of dry herb yielded 187 Gm. of oil, equivalent to 0.78 per cent.

The plant occurs in sandy soils from western Texas through New Mexico and Arizona and from southern Utah and Colorado to Mexico. It attracts large numbers of bees but the writers have no information whether nectar is obtained from it. The Indians appear to have a number of uses for the plant, as indicated by the following statement from *Uncultivated Native Plants Used as Sources of Food*, by Edward F. Castetter, University of New Mexico Bulletin, Biological Series, Vol. 4, No. 1, pages 42–43 (1935):

"This plant is dipped in salt water and eaten as food by the Hopi. The leaves are boiled and eaten; the flowers are rubbed, then used as a flavoring substance which Hopi say tastes like brown sugar."

The plot of 1.5 acres was established on the Tucson Nursery as a seed-increase planting in the spring of 1937 from transplants which had been grown in nursery seed beds. The plants grow rapidly, bloom profusely and produce seed throughout the growing season. As the plant has a sprawling, prostrate habit of growth which in time would make irrigation, cultivation and the harvesting of seed difficult, it has been the practice to prune the plants back each winter to within about one foot of the base. The new growth is produced rapidly in the spring and a round symmetrical plant is formed which does not become sprawling until late in the season.

Seed in the hull at the rate of 436 pounds per acre has been harvested. About 25 per cent of the hulls contain seed. As the seed scatters as it ripens continuously through the summer, its collection is accomplished by sweeping it up from the ground under the plants and then separating it from dirt and débris by means of a seed-cleaning machine.

The seed germinates readily and the plant can also be propagated from stem cuttings, rooted in sand beds in the greenhouse or in propagating frames.

The amount of herb cut from the area mentioned is not the maximum that may be expected because the stand was only fair and the growth only what had been produced that spring following winter pruning.

EXAMINATION OF THE OIL.

The oil is light brown in color becoming somewhat darker on standing. It has a minty, pennyroyal-like odor but the taste is without the characteristic "cooling" effect of peppermint. The specific gravity at 25° C. is 0.9339. It is soluble in all proportions of 95 and 80 per cent alcohol and in $1^1/_2$ volumes of 70 per cent alcohol. The angle of rotation in 100-mm. tube at 20° C. is +17.2°. The acid number is 2.11; saponification number 23.3 and acetylization number 42.5. Schiff's reagent revealed the presence of traces of aldehydes.

Following are the results of fractionating 100 cc. of the oil at atmospheric pressure:

Fraction	Temperature	Volume
1	—183° C.	2.5 cc.
2	183–200° C.	3.0 cc.
3	200–220° C.	76.0 cc.
4	above 220° C.	18.5 cc. (residue)
		100.0 cc.

Fraction 3 was again fractioned as follows:

Fraction	Temperature	Volume
1	−210° C.	10.0 cc.
2	210–216° C.	16.0 cc.
3	216–220° C.	38.0 cc.
4	220–220.5° C.	7.5 cc.
5		4.5 cc. (residue)
		76.0 cc.

The physical constants of fraction 3 from the refractionation were found to be:

Specific gravity at 25° C.	0.9328
Angle of rotation 100 mm. 20° C.	+24.6°
Index of refraction at 25° C.	1.4837

Inasmuch as the above constants correspond closely to those of pulegone it is obvious that pulegone is the principal constituent of the oil.

A COLLABORATIVE INVESTIGATION OF THE SPECTROPHOTOMETRIC METHOD FOR ASSAY OF VITAMIN A.*

BY C. L. BARTHEN, F. F. BERG, E. B. CARTER, D. M. COPLEY, R. J. FOSBINDER, T. LEWIS AND F. O. TAYLOR.[1]

At the combined A. D. M. A. and A. P. M. A. Contact Committee Meeting (held at the Washington Hotel, Washington, D. C., March 28, 1938) the Chairman of the Sub-Committee on Physical Tests read a report of a preliminary investigation showing to what extent, in six (6) different laboratories, the biological vitamin A assays of various fish liver oils parallel the spectrophotometric determination. The general discussion which followed the reading of the report was terminated by the acceptance of a proposal that the members of the Sub-Committee on Physical Tests and the members of the A. D. M. A. Vitamin Assay Committee (who were present) meet and outline a program for further study of this subject.

At the meeting of the combined committees, the Chairman of the Sub-Committee on Physical Tests was instructed to prepare a bulletin covering the suggested tentative program and submit copies of this bulletin to the members of both committees for their comments, corrections, etc.

In view of the report of the Vitamin Assay Committee (1) and the paper by Barthen and Leonard (2) and in accordance with the suggestions made in the replies to the bulletin, it was decided that six (6) samples be submitted for optical readings with various types of instruments, in as many laboratories as were willing and in a position to do so.

Inventors of physical instruments which are specially designed for the estimation of vitamin A (such as the photoelectric photometer, photoelectric colorimeter, monochrometer, spectrophotometer and vitameter) claim to achieve results by means of these instruments that are comparable with biological assays. Since the laboratories employing these various instruments expressed a willingness to collaborate, it seemed apparent that this study afforded an excellent opportunity to demonstrate whether or not, in the determination of vitamin A potency, the results obtained by physical instruments are as reliable as those obtained by biological assay.

The committee takes this occasion to express its sincere appreciation and gratitude to:

Atlantic Coast Fisheries Corp.	Mead Johnson & Co.
Distillation Products, Inc.	National Oil Products Co.

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* Read before the Scientific Section at the Twenty-eighth annual meeting of the American Drug Manufacturers' Association, The Homestead, Hot Springs, Va., May 1, 1939.

[1] Sub-Committee on Physical Tests.

Duke University
Electrical Testing Laboratories
The Fleischmann Laboratories
The Maltbie Chemical Co.
The Norwich Pharmacal Co.
Parke, Davis & Co.
The E. L. Patch Company
United Drug Co
White Laboratories, Inc.

for their gracious coöperation in this particular piece of research.

Procedure.—The following information, concerning the specimens, instructions, etc., were submitted to each laboratory coöperating in this investigation:

"It is our desire that the vitamin A potency of the specimens submitted be determined by any physical instrument suitable for the purpose. These specimens represent different kinds of fish liver oils or blends, covering a wide range of potency and having been biologically assayed at recent dates in different laboratories.

"The potencies given below are listed merely for the convenience of the operator and economy of material and labor:

No. 1. Less than 10,000 U. S. P. vitamin A units per Gm.
No. 2. Less than 10,000 U. S. P. vitamin A units per Gm.
No. 3. Between 25,000 and 100,000 U. S. P. vitamin A units per Gm.
No. 4. Between 25,000 and 100,000 U. S. P. vitamin A units per Gm.
No. 5. Between 150,000 and 400,000 U. S. P. vitamin A units per Gm.
No. 6. Between 150,000 and 400,000 U. S. P. vitamin A units per Gm.

"It is suggested that two samples of each specimen be weighed out and subjected to the optical determinations. In the event the readings of the two samples do not check within ±5 per cent, a third sample of the specimen should be submitted for reading. The average of the two readings that check each other within the limit set, and the conversion factor established for the particular instrument employed should be used in calculating the equivalent in U. S. P. units.

"It is requested that isopropanol (99 per cent) be used in making dilutions of the specimens submitted.

"The purpose of this collaborative investigation is either to prove conclusively that, when the proper conversion factors are employed, there is definite agreement in the results obtained in different laboratories with various instruments; or, in the event there are differences in the results, to ascertain whether these differences are significant when compared to the acknowledged variations in biological assays."

COMMENTS ON SPECIMENS.

The six samples sent out for these coöperative tests were identified by number only, with the statement in the accompanying letter as to the probable range of potency for each specimen. The actual identity and potencies as determined by bio-assays were as follows:

TABLE I.

No.	Description of Specimens.	U. S. P. Vitamin A Units per Gm.
1.	U. S. P. reference oil	3,000
2.	50 per cent dilution of U. S. P. reference oil (No. 1) with cottonseed oil	1,500
3.	Halibut liver oil	70,000
4.	50 per cent dilution of halibut liver oil (No. 3) with cod liver oil (destearinated)	35,000
5.	Distilled vitamin A ester product	300,000
6.	50 per cent dilution of distilled vitamin A ester product (No. 5) with cod liver oil (destearinated)	150,000

The unit values by bio-assay shown in this table were assigned on the basis of the following data:

1. The U. S. P. reference oil, used here as an unknown sample, is generally accepted as of 3000 unit value per Gm.
2. The U. S. P. reference oil diluted to half stregnth must therefore be 1500 units per Gm.

3. This halibut liver oil had been assayed three times in two laboratories and accepted as 70,000 units per Gm.
4. By calculation this sample, half the strength of No. 3, must be 35,000 units per Gm.
5. This sample was supplied by Dr. Hickman as of 300,000 units per Gm.
6. By dilution and calculation this sample must therefore be 150,000 units per Gm.

As a check on the dilutions and to ascertain whether the potencies assigned to the various specimens were correct, a sample of each specimen was again subjected to biological assay. Adequate quantities of each specimen were prepared to insure all investigators receiving identical samples. Data concerning these assays are given in Table II.

TABLE II.

Specimen No.	Description.	Unit Level Per Gm.	Amount Fed Daily, Mgm.	No. of Rats Wt. Gain 12–60 Gm.	Average Wt. Gain 12–60 Gm.	Date of Assay Report.
	U. S. P. reference oil (control)	3,000	1.2	9 of 10	41.3	8/12/38
1.	U. S. P. reference oil	3,000	1.2	8 of 10	34.6	8/12/38
2.	50 per cent dilution of U. S. P. reference oil with cottonseed oil	1,500	2.4	10 of 10	38.0	8/12/38
3.	Halibut liver oil, RM 1005	70,000	0.051429	10 of 10	37.0	8/12/38
4.	50 per cent dilution of halibut liver oil, RM 1005, with cod liqer oil (destearinated)	35,000	0.102857	8 of 10	35.1	8/12/38
5.	Distilled vitamin A ester product	300,000	0.012000	9 of 10	35.0	8/12/38
6.	50 per cent dilution of distilled vitamin A ester product with cod liver oil (destearinated)	150,000	0.024000	9 of 10	34.3	8/12/38

These final check biological assays were conducted in accordance with the U. S. P. method for vitamin A.

Although the specimens, recorded in Table II, were assayed in the same laboratory at the same time, it will be noted that the group of rats fed the U. S. P. reference oil as the positive control shows an average gain in weight of 41.3 Gm., whereas the group fed the U. S. P. reference oil submitted as specimen No. 1 shows an average gain in weight of 34.6 Gm. Apparently there is no accounting for this phenomenon other than the variation in biological response. Examination of data on U. S. P. reference oil accumulated in the laboratory that conducted the above-mentioned assays, shows the average gain in weight of 53 groups (each of 10 animals) run in the past 20 months is 37.1 Gm. with a standard deviation of 3.51 Gm. It is evident that the spread between these two groups may well occur.

The determination of vitamin A potency by biological assay is subject to many variable factors which may cause deviations in the results. From the many opinions expressed in the literature, a conservative estimate of the error in biological assays which may occur in any individual laboratory is approximately ±20 per cent or a spread of 40 per cent. However, the results of a series of assays, of the same material, conducted in six or more different laboratories, are likely to show a deviation of approximately ±30 per cent or a spread of 60 per cent. E. M. Hume (6) recently reported a collaborative study by 10 laboratories in which the results of the biological assays of the U. S. P. reference cod liver oil ranged from 1334 to 3270 I. U. of vitamin A per Gm., with a weighted mean of 2619 I. U. per Gm. This represents a deviation of −49.1 per cent and +24.9 per cent, or a spread of 74.0 per cent.

The preceding data justify the conclusion that the average response obtained with the U. S. P. reference oil, submitted as specimen No. 1, might properly be employed as the standard for comparison with the average response obtained with the other specimens.

In Table II it will be further noted that the responses of the groups fed specimens Nos. 2, 3, 4, 5 and 6, when compared with the response of specimen No. 1, are all within what may be considered the permissible limits of biological variation. Consequently, we are of the opinion that the vitamin A potencies assigned to the various specimens are sufficiently accurate for the purposes of this study.

Whether the potency as determined by a physical instrument represents the biological response as determined by a biological assay is a controversial subject, which has been discussed in many articles in the literature and at various scientific meetings. Furthermore, comparative studies of the spectrophotometric and biological assays for vitamin A have been conducted by a number of investigators: namely, Barthen and Leonard (2), Black, *et al.* (4), Pritchard, *et al.* (5), Hume (6). In addition there is a considerable amount of data on this particular subject, that is available although not yet published. In all of the studies mentioned, a great number of specimens, which represented a large variety of vitamin A bearing substances and a wide range of potencies, were employed. Therefore, for the purposes of this study, it was decided that a few representative specimens would be sufficient; but that as many types of instruments and as many laboratories as possible should be engaged in the project.

DATA CONCERNING THE SPECTROPHOTOMETRIC ASSAYS.

Laboratory No.	Instruments Employed in This Project.
1	Hilger Spectrophotometer.
2	Hilger Spectrophotometer.
3	Bausch & Lomb Spectrophotometer.
4	Hilger Vitameter.
5	Hilger Spectrophotometer.
6(s)	Hilger Spectrophotometer.
6(v)	Hilger Vitameter.
6(p)	Specially designed Photometer.
7	Specially designed Vitamin A Meter.
8(s)	Bausch & Lomb Spectrophotometer No. 748
8(v)	Hilger Vitameter (1938).
9	Evelyn Photoelectric Colorimeter.
10	Hilger Vitameter.
11	Hilger Spectrophotometer.
12	Hilger Vitameter with S-I Lamp.
13	Monochromator, Tungsten Light Source, Photocell Detector.

In the tabulations of data in Table III, the first seven lines are those obtained with spectrophotometers, the next four lines present data obtained with vitameters and the remaining lines cover data obtained by various specially designed instruments.

TABLE III.

		Equivalents in U. S. P. Units per Gm.					
Date.*	Lab. No.	Specimen No. 1.	Specimen No. 2.	Specimen No. 3.	Specimen No. 4.	Specimen No. 5.	Specimen No. 6.
6/12/38	1	3,060	1,776	62,274	32,528	289,328	151,298
6/15/38	2	3,128	1,754	65,900	34,200	302,500	156,600
8/22/38	5	2,875	1,692	54,517	29,999	279,316	135,475
8/12/38	6(s)	2,888	1,606	62,152	30,739	285,726	142,985
8/26/38	11	3,500	1,880	68,000	34,600	315,000	158,000
6/28/38	3	3,100	1,675	61,400	31,100	294,000	144,800
7/29/38	8(s)	3,310	1,726	60,736	29,536	271,144	147,264
6/20/38	4	3,186	1,572	59,558	32,525	277,728	157,978
6/14/38	6(v)	2,750	1,415	64,809	31,880	416,333	156,449
7/27/38	8(v)	3,099	1,674	61,984	30,680	272,792	139,360
8/23/38	10	2,943	1,659	59,428	32,271	278,414	139,314
6/15/38	6(p)	3,220	1,470	73,203	36,346	350,393	175,027
6/23/38	7	3,218	1,595	74,420	34,205	339,600	138,900
8/19/38	9	..	..	...	...	....	....
8/11/38	13	2,921	1,575	58,850	28,676	277,130	135,034
9/19/38	12	2,465	1,368	61,150	30,500	....	125,150
Totals		45,663	24,437	948,381	479,785	4,249,404	2,203,634

Averages	3,044	1,629	63,225	31,986	303,529	146,909
Bio-assays	3,000	1,500	70,000	35,000	300,000	150,000
Deviation of av. results from bio-assays	+44 +1.47%	+129 +8.6%	−6,775 −9.68%	−3.014 −8.61%	+3,529 +1.18%	−3,091 −2.06%
Greatest deviation from mean of results plus (+)	456 14.98%	251 15.41%	11,195 17.71%	4,360 13.63%	112,804 37.16%	28,118 19.14%
Greatest deviation from mean of results minus (−)	579 19.02%	261 16.02%	8,708 13.77%	3,310 10.35%	32,385 10.67%	21,759 14.81%
Spread	34.00%	31.43%	31.48%	23.98%	47.83%	33.95%

* Readings were made within a week before or after date given in table.

In Table III are shown the calculated equivalents in U. S. P. units, for the various specimens, as reported by the different laboratories. In compiling the data for this table no significance was given to any particular type of instrument employed in making the determinations; because, it was desired merely to reveal the extent of agreement in the results obtained with various instruments in different laboratories. Also to demonstrate to what extent the average potencies, as determined by physical instruments, deviate from the potencies determined by biological assay.

Laboratory No. 9 did not report any equivalents in U. S. P. units; consequently no results for this laboratory appear in this table.

Examination of Table III will reveal that the averages of the equivalents, obtained for the respective specimens, approximate the potencies indicated by the biological assays. However, the results obtained in some of the laboratories, in one or more instances, are so far out of line with the other results obtained with the same specimen, as to make the deviations from the mean and the spread of results with each specimen unduly great. Elimination of the highest and lowest equivalents from the calculations would reduce the percentage spread of results, given in Table III, considerably. For examples:

With Specimen No. 1: Elimination of the two extremes would reduce the percentage spread from 34.00 per cent to 18.34 per cent.

With Specimen No. 2: Elimination of the two extremes would reduce the percentage spread from 31.43 per cent to 22.15 per cent.

With Specimen No. 3: Elimination of the two extremes would reduce the percentage spread from 31.48 per cent to 22.77 per cent.

With Specimen No. 4: Elimination of the two extremes would reduce the percentage spread from 23.98 per cent to 15.87 per cent.

With Specimen No. 5: Elimination of the two extremes would reduce the percentage spread from 47.83 per cent to 26.14 per cent.

With Specimen No. 6: Elimination of the two extremes would reduce the percentage spread from 33.95 per cent to 15.69 per cent.

The average spread calculated from Table III is 33.78 per cent. With the elimination of the extremes the average spread would be 20.16 per cent.

In Table IV are shown the average E. values, for the various specimens, as reported by the different laboratories. This table is divided into three parts so that comparisons of the results may readily be made as to variations between laboratories employing the Spectrophotometers, the Hilger Vitameter and the specially designed instruments.

Laboratories No. 6(p) and No. 12 did not report any E. values; consequently no results for these laboratories appear in the table.

The E. values reported by laboratory No. 7 are omitted from this table, because they were determined at the wave-length of 3303 Angstrom units, and it is the conclusion of this laboratory that this difference in wave-length of light used affects the results to so great an extent that they may not fairly be compared with the E. values reported by the other laboratories and determined at 3280 Angstrom units.

As specimen No. 1 represents the U. S. P. reference cod liver oil, it was believed to be expedient to determine to what extent the conversion factors, employed by the collaborating laboratories, differed from the conversion factors calculated from the E. values reported for this specimen.

In Table V are shown:

A. The conversion factors reported and employed in calculating the equivalent in U. S. P. units per Gm.

B. The corrected conversion factors calculated from the E. values reported for specimen No. 1.

%±. The deviation in percentage, of A from B.

It will be noted that the deviations extend from minus 4.19 per cent to plus 16.77 per cent. (Laboratory No. 4 reported 2 conversion factors. See remarks under General Discussion.)

TABLE IV.

Date.*	Lab. No.	Average E. Values					
		Specimen No. 1.	Specimen No. 2.	Specimen No. 3.	Specimen No. 4.	Specimen No. 5.	Specimen No. 6.
		Spectrophotometer.					
6/12/38	1	1.43	0.83	29.1	15.2	135.2	70.7
6/15/38	2	1.58	0.886	33.3	17.25	152.8	79.1
8/22/38	5	1.495	0.880	28.35	15.6	145.25	70.45
8/12/38	6(s)	1.51	0.909	29.29	14.565	134.09	67.18
8/26/38	11	1.66	0.89	32.2	16.40	149.0	74.9
6/28/38	3	1.55	0.838	30.7	15.55	147.0	72.4
7/29/38	8(s)	1.59	0.83	29.2	14.2	130.5	70.8
Average	(of 7)	1.545	0.866	30.31	15.54	141.98	72.22
		Hilger Vitameter.					
6/20/38	4	1.54	0.76	28.2	15.4	131.5	74.8
6/14/38	6(v)	1.593	0.901	34.646	16.731	(215.7)[1]	81.67
7/27/38	8(v)	1.49	0.805	29.8	14.75	131.15	67.0
8/23/38	10	1.375	0.775	27.77	15.08	130.1	65.1
Average	(of 4)	1.50	0.810	30.10	15.49	130.9	72.14
		Special Instruments.					
6/15/38	6(p)	..	..	..	..	..	..
8/19/38	9	..	..	29.5	14.6	147.0	72.6
8/11/38	13	1.365	0.736	27.5	13.4	129.5	63.1
6/23/38	7	..	..	..	..	..	..
9/22/38	12	..	..	..	..	..	..
Average	(of all)	1.515	0.837	29.97	15.29	138.59	71.52
Greatest deviation from mean of results plus (+)		0.145	0.72	4.676	1.96	14.21	10.15
		9.57%	8.60%	15.60%	12.82%	10.25%	14.19%
Greatest deviation from mean of results minus (−)		0.150	0.101	2.47	1.89	9.09	8.42
		9.90%	12.07%	8.24%	12.36%	6.56%	11.77%
Spread		19.47%	20.67%	23.84%	25.18%	16.81%	25.96%

The average spread calculated from Table IV is 21.99 per cent.

* Readings were made within a week before or after date given in table.

[1] Omitted from calculations.

Laboratories Nos. 6(p), 9 and 12 did not report any E. values or conversion factors for specimen No. 1; consequently no results of calculations for these laboratories appear in Table V. In the case of laboratory No. 6(v) the corrected conversion factor was calculated from the E. values reported.

In view of the preceding data, it was deemed advisable to ascertain whether the results

(equivalents in U. S. P. units) obtained by employing the corrected conversion factors, would be in closer agreement than the results obtained by employing the conversion factors established in and reported by the different laboratories. Therefore, in Table VI are shown the equivalents in U. S. P. units, obtained by multiplying the reported E. values, for the various specimens, by the corrected conversion factors (see B in Table V).

TABLE V.

Laboratory No.	Conversion Factors. A.[1]	B.[2]	% ±.[3]
1	2140	2098	+ 2.00
2	1980	1899	+ 4.27
5	1923	2007	− 4.19
6(s)	1920	1987	− 3.37
11	2110	1807	+16.77
3	2000	1936	+ 3.31
8(s)	2080	1887	+10.23
4	2069	1948	+ 6.21
4	2112	1948	+ 8.42
6(v)	..	1883	...
8(v)	2080	2014	+ 3.28
10	2140	2182	− 1.93
6(p)	..	..	...
7	2780	2591	+ 7.29
9	..	..	...
13	2140	2198	− 2.64
12	..	..	...

[1] The reported conversion factors.
[2] The corrected conversion factors.
[3] The deviation, in percentage, of A from B.

Laboratories Nos. 6(p), 9 and 12 were omitted from this table for the same reason as mentioned under Table V.

TABLE VI.

Laboratory No.	Equivalents in U. S. P. Units Per Gm. Specimen No. 1.	Specimen No. 2.	Specimen No. 3.	Specimen No. 4.	Specimen No. 5.	Specimen No. 6.
1	3,000	1,741	61,052	31,890	283,650	148,329
2	3,000	1,683	63,237	32,758	290,167	150,211
5	3,000	1,766	56,898	31,309	291,517	141,393
6(s)	3,000	1,806	58,199	28,941	266,437	133,487
11	3,000	1,608	58,185	29,635	269,243	135,344
3	3,000	1,622	59,435	30,105	284,592	140,166
8(s)	3,000	1,566	55,100	26,795	246,254	133,600
4	3,000	1,480	54,934	29,999	256,162	145,710
6(v)	3,000	1,697	65,246	31,503	406,163	153,785
8(v)	3,000	1,621	60,017	29,707	264,136	134,938
10	3,000	1,691	60,594	32,905	283,660	142,048
6(p)	..	..	...	...	....	....
7	3,000	1,487	69,361	31,947	316,517	129,472
9	..	..	...	...	....	....
13	3,000	1,618	60,445	29,453	284,641	138,694
12	..	..	...	...	....	....
Total	39,000	21,386	782,703	396,947	3,743,139	1,827,177

Table VI.—(*Continued from page 667.*)

Averages	3,000	1,645	60,208	30,534	287,934	140,552
Bio-assays	3,000	1,500	70,000	35,000	300,000	150,000
Deviation of av. results from bio-assays	..	+145	−9,792	−4,466	−12,066	−9,448
	..	+8.81%	−16.26%	−14.63%	−4.19%	−6.72%
Greatest deviation from mean of results plus (+)	..	161	9,153	2,371	118,229	13,233
	..	9.79%	15.20%	7.77%	41.06%	9.42%
Greatest deviation from mean of results minus (−)	..	165	5,274	3,739	41,680	11,080
	..	10.03%	8.76%	12.25%	14.48%	7.88%
Spread	..	19.82%	23.96%	20.02%	55.54%	17.30%

The average spread calculated from Table VI is 27.33 per cent.

Table VI illustrates to what degree the corrected conversion factors affect the calculated potencies of the different specimens in the individual laboratories; also demonstrates to what extent the corrected factors influence the statistical calculations. It will be noted in this table that the averages of the equivalents, for the respective specimens, do not approximate the potencies indicated by the biological assays as well as those in Table III.

A comparison of Tables III and VI will reveal that, with the exception of specimen No. 5, the calculated equivalents in Table VI are in closer agreement than those in Table III. Furthermore, with the elimination of the extreme results obtained with specimen No. 5 from both tables, the spread for this specimen would then be less in Table VI than in Table III.

Upon further examination of Table III, it is evident that some of the laboratories obtained results which show a much greater spread of deviation from the averages than other laboratories whose results are more in line with the averages or otherwise more consistently high or low.

Table VII shows to what extent, in per cent, each laboratory deviates from the average equivalent given in Table III for each specimen; also shows the spread of deviations in each laboratory.

In this table it will be noted that seven laboratories, namely Nos. 5, 8(s), 4, 6(v), 6(p), 7 and 12 show a spread greater than 15 per cent, which would indicate unreliability due to the technique or instrument employed in making the determinations. It therefore seemed that it would be interesting and informative to determine another set of averages, on the basis of the equivalents as shown in Table III, from the eight remaining laboratories only.

TABLE VII.

Per Cent Deviation from Average.

Laboratory No.	Specimen No. 1.	Specimen No. 2.	Specimen No. 3.	Specimen No. 4.	Specimen No. 5.	Specimen No. 6.	Spread of Deviations.
1	+ 0.5	+ 9.0	− 1.5	+ 1.7	−4.7	+ 3.0	13.7
2	+ 2.8	+ 7.7	+ 4.2	+ 6.9	− 0.3	+ 6.6	8.0
5	− 5.6	+ 3.9	−13.8	− 6.2	− 8.0	− 7.8	17.7
6(s)	− 5.1	− 1.4	− 1.7	− 3.9	− 5.9	− 2.7	4.5
11	+15.0	+15.4	+ 7.6	+ 8.2	+ 3.8	+ 7.5	11.6
3	+ 1.8	+ 2.8	− 2.9	− 2.8	− 3.1	− 1.4	5.9
8(s)	+ 8.7	+ 6.0	− 3.9	− 7.7	−10.7	+ 0.2	19.4
4	+ 4.7	− 3.5	− 5.8	+ 1.7	− 8.5	+ 7.5	16.0
6(v)	− 9.7	−13.1	+ 2.5	− 0.3	+37.2	+ 6.5	50.3
8(v)	+ 1.8	+ 2.8	− 2.0	− 4.1	−10.1	− 5.1	12.9
10	− 3.3	+ 1.8	− 6.0	+ 0.9	− 8.3	− 5.2	10.1
6(p)	+ 5.8	− 9.8	+15.8	+13.6	+15.4	+19.1	28.9
7	+ 5.7	− 2.1	+17.7	+ 6.9	+11.9	− 5.5	23.2
13	− 4.0	− 3.3	− 6.9	−10.3	− 8.7	− 8.1	7.0
12	−19.0	−16.0	− 3.3	− 4.6	..	−14.8	15.7

Table VIII shows the average equivalent in U. S. P. units of the eight selected laboratories, for each specimen; this table also gives, for each laboratory, the per cent deviation from the mean for each specimen, the average deviation and the new spread.

TABLE VIII.

	Specimen No. 1.	Specimen No. 2.	Specimen No. 3.	Specimen No. 4.	Specimen No. 5.	Specimen No. 6.	Average Per Cent Deviation.	Per Cent Spread.
Averages	3,080	1,700	62,499	31,849	289,361	145,924	...	...
Lab. No. 1	− 0.6	+ 4.5	−0.4	+ 2.1	0	+3.7	+1.6	5.1
Lab. No. 2	+ 1.6	+ 3.2	+5.4	+ 7.4	+4.5	+7.3	+4.9	5.8
Lab. No. 6(s)	− 6.2	− 5.5	−0.6	− 3.5	−1.3	−2.0	−3.2	5.6
Lab. No. 11	+13.6	+10.6	+8.8	+ 8.6	+8.9	+8.3	+9.8	5.3
Lab. No. 3	+ 0.6	− 1.5	−1.8	− 2.4	+1.6	−0.8	−0.7	4.0
Lab. No. 8(v)	+ 0.6	− 1.5	−0.8	− 3.7	−5.7	−4.5	−2.6	6.3
Lab. No. 10	− 4.4	− 2.4	−4.9	+ 1.3	−3.8	−4.5	−3.1	6.2
Lab. No. 13	− 5.2	− 7.4	−5.8	−10.0	−4.2	−7.5	−6.7	5.8

It was demonstrated that the results of the calculations given in Tables V and VI did not accomplish the hoped for explanation or correction of the wide discrepancies in the results obtained in some of the laboratories. Consequently, further analysis of the preceding data was indicated. The next step was to make a correction, by means of the average deviations in Table VIII, of the conversion factors used and reported by the eight laboratories under consideration.

In Table IX are shown:

A. The conversion factors reported and employed in calculating the equivalent in U. S. P. units per Gm.

B. The corrected conversion factors calculated from the E. values reported for specimen No. 1.

C. The corrected conversion factors obtained by adding to or subtracting from the reported factors, a figure representing the average per cent deviation given for each laboratory in Table VIII.

TABLE IX.

	Conversion Factors.		
Laboratory No.	A.[1]	B.[2]	C.[3]
1	2140	2098	2106
2	1980	1899	1883
6(s)	1920	1987	1981
11	2110	1807	1903
3	2000	1936	2014
8(v)	2080	2014	2134
10	2140	2182	2206
13	2140	2198	2283

[1] The reported conversion factors.

[2] The corrected conversion factors calculated from E. values for specimen No. 1.

[3] The conversion factors corrected by means of the average deviations.

TABLE X.

	Equivalents in U. S. P. Units per Gm.					
Laboratory No.	Specimen No. 1.	Specimen No. 2.	Specimen No. 3.	Specimen No. 4.	Specimen No. 5.	Specimen No. 6.
1	3,012	1,748	61,285	32,012	284,731	148,894
2	2,975	1,668	62,704	32,482	287,722	148,945
6(s)	2,991	1,801	58,023	28,853	265,632	133,084
11	3,159	1,694	61,277	31,209	283,547	142,535
3	3,122	1,688	61,830	31,318	296,058	145,814
8(v)	3,180	1,718	63,593	31,477	279,874	142,978
10	3,033	1,710	61,261	33,266	287,001	143,611
13	3,116	1,680	62,783	30,592	295,649	144,057
Totals	24,588	13,707	492,756	251,209	2,280,214	1,149,918

TABLE X.—(*Continued from page 669.*)

Averages	3,074	1,713	61,595	31,401	285,027	143,740
Bio-assays	3,000	1,500	70,000	35,000	300,000	150,000
Deviation of av. results from bio-assays	74 +2.47%	213 +14.20%	8,405 −12.01%	3,599 −10.28%	14,973 −4.99%	6,260 −4.17%
Greatest deviation from mean of results plus (+)	106 3.45%	88 5.14%	1,998 3.24%	1,865 5.94%	11,031 3.87%	5,205 3.62%
Greatest deviation from mean of results minus (−)	99 3.22%	45 2.63%	3,572 5.80%	2,548 8.11%	19,395 6.80%	10,656 7.41%
Spread	6.67%	7.77%	9.04%	14.05%	10.67%	11.03%

The average spread calculated from Table X is 9.87 per cent.

In Table X are shown the equivalents in U. S. P. units obtained by multiplying the E. values, reported by the eight selected laboratories for the various specimens, by the corrected conversion factors under C in Table IX.

It will be noted that in this table the calculated equivalents are in close agreement.

An examination of the tables will reveal that in Table X the deviations from the mean and the spread of results for each specimen are very much less than those in Tables III, IV and VI. For convenience in making a quick comparison, the average spreads, in per cent, are:

	Per Cent.		Per Cent.
Table III	33.78	Table VI	27.33
Table IV	21.99	Table X	9.87

GENERAL DISCUSSION.

Remarks submitted in the reports of some of the collaborators and the comments on them may afford a better interpretation of the results given in the various tables.

Laboratory No. 4 states: "In this Laboratory the average conversion factor for oils of a potency greater than 10,000 A per Gm., or for the unsaponifiable fraction of oils of a lower potency has been found to be 2112. The average conversion factor for the direct determination of oils lower than 10,000 A per Gm has been found to be 2069. In these calculations, both factors have been reported, as we could not tell in specimens 1 and 2 which was whole oil and which a solution of a non-saponifiable portion.

"Specimen No. 4. Run at two different temperatures to see what effect this would have."

As specimens Nos. 1 and 2 represent whole oils of potencies less than 10,000 units, the conversion factor of 2069 was employed in calculating the equivalents for these specimens, and the conversion factor 2112 was employed in calculating the equivalents of the other specimens given in Table III.

Laboratory No. 4 made determinations of specimen No. 4 at temperatures of 24° C. and 32° C.; the results obtained at these temperatures were the same. The temperatures at which the different laboratories conducted their determinations varied from 22.5° C. to 32° C. (72.5° F. to 90° F.). The temperatures may have influenced the results in some of the laboratories, yet there is no direct evidence to prove that the discrepancies in the results were due to temperatures at which the readings were made.

Laboratory No. 5 states: "Sample No. 2 did not give a good vitamin A absorption curve, absorbing quite strongly below 3000 A. Undoubtedly this increases the absorption at the vitamin A maximum 3280 A. A biological test would probably show less vitamin A potency than the optical test."

Evidence submitted by Haines and Drummond (3) led to the belief that the presence of a vegetable oil in combination with a vitamin A bearing oil may influence the shape of the absorption curve and be responsible for a false evaluation of the blend. Therefore, a product of this type was intentionally included in the group of specimens for this study.

It will be noted that 12 of the 15 equivalents in Table III and 11 of the 13 equivalents given in Table VI and all of the equivalents in Table X for specimen No. 2 show a greater potency than indicated by biological assay. However, when determinations were made on the unsaponifiable

fraction of this specimen, in two different laboratories, the equivalents in U. S. P. units were 1548 and 1530. These results check the biological assay.

Laboratory No. 6(s) states: " 'Uncorrected' values are simply the product of E. value × 1920; 'corrected' values are this product corrected for irrelevant absorption by our abritrary formula. This formula was worked out for the vitameter when used under certain conditions, but I am not at all sure it is applicable here.

"We consider 1600 the proper factor for International Units, 1920 the factor for the present issue of U. S. P. Reference Oil, the true potency of which is nearer 2500 I. U. than 3000."

Only the average of the corrected values are given in Table III; furthermore, the corrected values are in closer agreement with the mean of all the equivalents in this table than the uncorrected values.

Laboratory No. 6(v) states: " 'Corrected' values were derived from 'uncorrected' by our formula, with which you are familiar. Values were determined on the oils directly, without saponification. We do not use the E. value factor method, but instead use a calibration graph of the vitameter plotted against a series of dilutions of U. S. P. Reference C. L. O. Thus we avoid the controversy over what is the correct factor."

Only the average of the corrected values is given in Table III; however, with four of the six specimens, the uncorrected values were in closer agreement with the mean of all the equivalents in this table than the corrected values for the same specimens.

Laboratory No. 6(p)—only the average of the corrected values is given in Table III. However, all of the uncorrected values are in closer agreement with the mean of all the equivalents in this table than the corrected values.

Laboratory No. 8(v) states: "The conversion factor is based on a large series of 'E.' determinations made with the U. S. P. reference cod liver oil, giving an average E. value of 1.44."

In Table IV it will be noted that this laboratory obtained with specimen No. 1 an E. value of 1.59 when it employed the spectrophotometer and an E. value of 1.49 when it employed the vitameter; for both instruments the same conversion factor was employed. Therefore, a difference in the calculated equivalents is to be expected. In the event the E. value of 1.59 is correct for specimen No. 1 the conversion factor should be 1887 (see Table V). The equivalents obtained in Laboratory No. 8 with the vitameter are in closer agreement with the mean of all the equivalents give in Table III than the equivalents obtained with the spectrophotometer. Employment of the corrected conversion factors (in Table V) does not bring the equivalents into closer agreement with the mean of results.

The figures given in this discussion will indicate that either the E. value for specimen No. 1 found by the spectrophotometer (in this laboratory) or the conversion factor reported, is incorrect.

Laboratory No. 10 states: "*Time Factor:* The assays were all made within 15 minutes after the solution was prepared.

"You will note that both the 'readings' and the 'E. values' for each sample checked within significantly less than ±5 per cent. In order that you may be able to check the 6 samples against the U. S. P. reference cod liver oil, which we procured from Professor Cook, we made an assay of it, using isopropanol, for vitamin A simultaneously with the assay of your samples. Our results are reported above."

This laboratory obtained an average E. value of 1.40 with the reference cod liver oil as a positive control and an average E. value of 1.375 with the reference cod liver oil as an unknown. The two results are in such close agreement that no further comment is necessary.

Laboratory No. 12 states: "The results reported were obtained with a vitameter equipped with an S-1 lamp in place of the copper arc, the readings being recorded photographically at 0.05 scale intervals. The instrument was standardized by plotting vitameter scale values against U. S. P. reference cod liver oil concentrations. The vitamin A content in U. S. P. units per Gm. in the unknown sample was calculated by application of the following formula:

$$\frac{\text{A units per ml. (obtained from the calibration curve)} \times 100}{\text{Concentration of sample in per cent}} = \text{vitamin A units per Gm.}"$$

In three of the five specimens, the equivalents obtained in this laboratory deviate considerably from the mean of all equivalents obtained in Table III for the same specimens. As no E.

values or conversion factors were reported by this laboratory no satisfactory comparisons can be made with the results obtained in the other laboratories.

It has been suggested that the U. S. P. adopt a spectrophotometric method for the determination of the vitamin A content of cod liver oil and other fish liver oils, as an alternate for the biological assay. However, the opinion persists that vitamin A-bearing oils can be adulterated with some substance which would so influence the optical absorption that the number of units, determined by means of a physical instrument, would be greater than the number of units determined by a biological assay.

In view of the acknowledged wide deviation in biological response, the nature of which prohibits accurate control, a supplier of a vitamin A-bearing oil should not be obliged to depend entirely upon the results of a biological assay. Nevertheless, to prevent deliberate or even unintentional fraud, it is suggested that a supplier be compelled to guarantee that a check biological assay of his product, whether it was standardized by means of a spectrophotometric or biological assay, will be a success at a level of not less than 75 per cent of the claimed potency. It is believed that the adoption of the above suggestion will practically obviate any controversy or litigation as to the accuracy, reliability or validity of a bio-assay.

SUMMARY.

In the determination of vitamin A potency by physical instruments, it is apparent that the conversion factor is of paramount importance.

To achieve the greatest degree of accuracy in results, the E. value, of the U. S. P. reference oil, its unsaponifiable fraction and/or any other suitable standard, should be determined every day and the conversion factor calculated to check the constancy of conditions necessary for accurate operation of the instrument. In this manner, errors due to conditions in the laboratory, the instrument or the human element, can be obviated or at least reduced to a minimum. However, it is obvious that expertness, as a consequence of experience in the technique and knowledge of the fundamental principles of the instruments, is an essential factor for the attainment of accurate results.

Under specified and well controlled conditions of operation of the physical instruments, capable of accuracy of measurement, results can and should be obtained which are in closer agreement than those obtainable by biological assay.

When there is any doubt or question as to the source of the oil under consideration, the optical determination should be made on the unsaponifiable fraction.

The suggestion that a spectrophotometric method be adopted as an alternate for the biological assay, is discussed.

REFERENCES.

(1) Holmes, A. D., Black, A., Eckler, C. R., Emmett, A. D., Heyl, F. W., Neilson, C., and Quinn, E. J.: "The Practical Application of the Spectrophotometric Method for Assay of Vitamin A," JOUR. A. PH. A., 26, 525 (1937).

(2) Barthen, C. L., and Leonard, C. S., "A Comparison of Spectrophotometric and Biological Assays for Vitamin A," JOUR. A. PH. A., 26, 515 (1937).

(3) Haines, R. T. M., and Drummond, J. C., "The Use of Mammalian (Whale) Liver Oils and Concentrates in the Preparation of Artificial or 'Reinforced' Halibut Liver Oils." Released by Department of Physiology, Pharmacology and Biochemistry, University College, London, February 23, 1938.

(4) Black, A., Greene, R. D., Sassaman, H. L., and Sabo, C., "A Comparative Study of the Colorimetric, Vitameter and Biological Tests for Vitamin A," JOUR. A. PH. A., 27, 199 (1938).

(5) Pritchard, H., and Wilkinson, H., "A Discrepancy between Biological Assays and Other Methods of Determining Viatmin A," *Biochem. J.*, 31, 259 (1937).

(6) Hume, E. M., "Estimation of Vitamin A," *Nature*, 143, 22 (1939).

A NEED FOR AN ASSOCIATION OF EXCLUSIVE PRESCRIPTION PHARMACISTS.*

BY A. L. MALMO.[1]

The general trend of the drug business from the old apothecary shop, then to the ordinary drug store, followed by the chain store and now the cut-rating pine boards has about dropped Pharmacy to the depths of nowhere. The A. PH. A., a splendid organization, has done its utmost to keep it aloft but the good ship Pharmacy is destined to sink unless help is offered soon. In recent years, in each issue of the leading pharmaceutical journals, articles have been appearing relative to professional pharmacy. Many new graduates are gravely concerned about their future. On entering the drug field, the professional atmosphere falls so very short of their expectations. For years they have been told that a druggist was more than a merchant, that his professional standing would be equal to that of his companion professions, namely, the medical and dental. In other words, he was proud to be a pharmacy student. On passing the State Board he is thrown into the whirlpool of competitive general merchandising. His hours are long and tedious; working nights, holidays and Sundays, he soon discovers that his chosen career is not as pretty as painted. This, added to the usual small salary the first few years, makes the average young man wonder what it is all about.

Fortunately, for those who are especially interested in Pharmacy and are professionally minded, there is an opportunity for them in either hospital or professional pharmacy work. Recognized hospitals are gradually becoming Pharmacy conscious. Their standards now provide for the pharmacy to be in charge of a registered pharmacist. This is a mighty important step as it not only provides employment for many men and women but it automatically places Pharmacy on a higher plane. The recent hospital pharmacist internship plan has placed young pharmacists in a splendid position to help Pharmacy. If these positions are held by representative professionally-minded young men, they can do a splendid job for Pharmacy by closely contacting medical internes in an effort to encourage and teach prescription writing.

In communities where these internships are now available and used, it would be a fine gesture on the part of the older professional pharmacist to aid the younger one by offering the benefit of his experience. If this were done throughout the nation, the younger generation of physicians would have a great deal more respect for our profession. The various hospital pharmacists' organizations throughout the country are doing a tremendous lot of work for Pharmacy and should be further encouraged by all employers of former hospital pharmacists who are still interested in that phase of our work. Their hospital experience is valuable to all professional pharmacists.

In the last twenty years or so, many pharmacists have been brave enough to enter the field of so-called "exclusive prescription pharmacists." The great majority have been quite successful and they are deserving of their success and position by their untiring efforts to promote professional pharmacy.

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* Presented before the Conference of Professional Pharmacists, A. PH. A., Atlanta meeting, 1939.

[1] Pharmacist, Duluth, Minn.

Now with the rapid increase of professional shops, I believe an association should be perfected, incorporating the highest ideals of standards known to Pharmacy, memberships to be limited to exclusive prescription stores which in turn will be strictly governed by a rigid Code of Ethics. The A. M. A., a successful and well-thought-of association, owes its success to its high ethical standards. Were it not for the strict enforcement of their national, state and local regulations they soon would be as unprofessional as many among the ranks of modern druggists. Picture, if you can, the position Pharmacy would enjoy to-day had a Code of Ethics been established and maintained when Pharmacy was in its infancy, and during succeeding years.

The A. M. A., recently, I understand, considered certifying a list of pharmacists, especially in the larger centers, as a protection for public health and A. M. A. member prescribers. Let us relieve the A. M. A. of this task and responsibility, or better yet, let us ask them for their assistance in setting our standards high enough to warrant certification or membership in a professional organization. Adopting their standards would automatically give us their seal of approval, which is really what we are seeking. Then it is up to us to live up to these ideals and, as we grow older, gain the respect of the entire medical profession.

The organization among other things should include the following in its Code of Ethics: (*a*) Having foremost in mind the matter of public health; (*b*) A registered pharmacist always in charge of the pharmacy; (*c*) Close coöperation with all allied professions, especially medical, by, 1, no counter prescribing; 2, discouraging self medication; 3, ethical advertising; 4, activities confined to prescription dispensing and sale of only physician, hospital and sick-room supplies; 5, members must be registered pharmacists owning own stores; 6, encourage the prescribing of more U. S. P. and N. F. preparations.

Discourage the prescribing of proprietaries, especially in the case where a manufacturer develops a certain chemical and then combines it with all other drugs and chemicals in the U. S. P., which not only makes the price prohibitive but encourages dispensing by many physicians or tends to make the trade name so common the physician often recommends the product and it often becomes an over-the-counter item. When a combination of drugs is necessary it is the job of the pharmacist to prepare the prescription and not have to purchase same from the manufacturer made in capsules or tablets in all pretty pastel shades.

The manufacturers have stayed awake nights competing with each other in an attempt to place the dispensing pharmacist in the rôle of a "pill and capsule counter" or a "liquid pourer outer" from one bottle to another.

As an example of the above-mentioned prohibitive price, let us take a well-known capsule which consists of theobromine, potassium iodide and sodium salicylate. They cost us to dispense, including pharmacists' time, 82 cents for 125. The wholesale price is $2.75.

Then, too, the manufacturer changes his size, color or general make-up of his preparation too often, necessitating an explanation to the patient which is not always accepted so willingly by the everlasting suspecting public.

Membership would be entitled to a certified professional pharmacy emblem, loaned to the pharmacist for duration of membership and to be returned upon request of board of governors when found guilty of violation of Code of Ethics. Em-

blems should be used on all advertising copy, labels, windows, stationery and delivery cars.

The public and medical profession are entitled to be certain their prescriptions are being filled by a registered pharmacist. This they can be assured of in any store bearing the above-mentioned emblem. Some state boards have not been as active as the law allows in apprehending many violators of pharmacy laws with the result that many more pharmacists are trying to conduct their stores without being covered with registered pharmacists. Pharmacy always suffers when this happens. An organization of this type can encourage pharmacists in other communities to throw out the commercial lines and practice Pharmacy as it was intended. Cities of 5000 or more can well support a professional pharmacy.

While most prescription shops enjoy a fine prescription business, there are still many physicians who do not quite appreciate the value of professional pharmacists and allow their prescriptions to fall where they may. They do not quite recognize, first of all, the professional interest imbued in professional pharmacists. Few appreciate the time and expense required in preparing the following:

Pharmaceutical library, professional and ethical advertising, professional cooperation, professional service, professional knowledge, and last but not least, professional ability.

The exclusive prescription stores which dispense the majority of the nation's prescriptions are entitled to more coöperation from the pharmaceutical manufacturers. There are too many duplications on the market and in many instances the prescription prices quoted by detail men are ridiculous. We should establish a reasonable mark-up and notify each manufacturer that it will be used. As it is, no two detail men now quote the same price in any city. Manufacturers should be told to put a stop price on their entire line to the Physicians and should be asked to stop selling direct to them. A National prescription price schedule should be formulated by a committee. We owe it to the public, the medical profession and ourselves to perfect an organization which will keep Pharmacy professional.

We should have the full support of all colleges of pharmacy, since they more or less hold the future of our profession in the palm of their hands. They should discourage all young men and women whom they believe not to be professionally minded from finishing pharmacy. It would take hours to enumerate the advantages of this organization. I have touched on only important factors. We have all to gain and nothing to lose by association.

I truthfully hope that an organization is started at this convention. I recommend that a committee be appointed to make a further study of this and be empowered to call another Conference of Professional Pharmacists if they deem it advisable, before the closing days of this fine meeting.

Vitamins are replacing sleeping medicines in the newest treatment of insomnia or sleeplessness, reported by Dr. Louis J. Karnosh, Western Reserve School of Medicine, Cleveland, according to the *Jour. A. M. A.* for September 30th. The vitamin treatment may, in fact, be looked on as a cure, since it attacks an underlying cause of the condition, whereas the sleeping medicines are palliative.

THE PROFESSION AND THE COUNTRY DRUG STORE.*

BY CHARLES E. WILSON.[1]

So far as this article is concerned, the phrase "Country Drug Store" is used for the purpose of comparison, and refers to those stores located in the rural sections, the small towns, the smaller cities and the suburbs of most of the metropolitan districts. These stores are selected because they are believed to be in the majority numerically, and as a result come much nearer serving the nation than does the real city store.

Professional Equipment.—The physical and orderly appearance of the country store seems to compare favorably with that of the city store. The stock investment, considering the population served, will in many instances be more varied and in larger quantities than the city store for the reason that the source of supply is usually further away from the country store, while it is close by for the city store, thus it may be beneficial to each. The country store perhaps stocking a greater quantity, may be able to secure discounts which would not be practical to the city store because of its inability to use such quantities. The operation of the country store looks upon the big city store as being the reward for supreme effort and professional ability. He thinks that the city stores all have big prescription business and have the equipment necessary to carry out most operations; but, have they?

It would seem that in country or city the average store has only such equipment as is necessary to get by with. There are seldom enough graduates; too frequently they are not accurate because they were bought for price. How many graduated percolation jars, tablet trituate molds, suppository molds, collapsible tubes, retort stands, filter papers, hot plates, homogenizers, mixing machines, will you find in the country or city drug store? If you locate a funnel the chances are that it is made of tin and is rusty from use and disuse.

The country drug store pharmacist lays a lot of oral stress upon the prescription end of the business when talking with a customer in an apparent effort to advertise, yet he has his prescription desk pushed into the dark corner of the store where it cannot be seen and where it can be used for storage room and will not have to be kept clean. It is usually of the one-man type store, meaning, of course, that the registered man in the store is usually the proprietor and it is not often there are two registered men in the store. These stores usually have a small amount of professional business; consequently they work from one part of the store to another. Their time is consumed in various and sundry ways so peculiar to the retail drug business, and as a result their professional interest is usually of the passive type. In other words, they are always going to do this or that, yet they seldom get around to it.

Ability to Promote Professional Work.—A close study of the country drug store with its registered man will reveal that he has had about the same standard training; has passed about the same type state board examination as has the city pharmacist. Basically his ability should be on a par with the city man. Naturally there are some who are misfits and have to be classed as poor. In most instances

* Presented before the Section on Practical Pharmacy and Dispensing, A. PH. A., Atlanta meeting.

[1] Retail Pharmacist, Corinth, Miss.

this is an individual matter and is no reflection upon the training received. Generally they do have ability and initiative, even though it may be latent.

Time Element Necessary for Professional Work.—The average country drug store usually has more time at its disposal than the city store with the continuous stream of traffic that must be handled. There are certain seasons of the year when general business for the country store is at low ebb, but we find that illness is no respecter of seasons and people get sick then as well as when the commercial aspects present a red glow from acceleration of a big sale that produces much traffic and less profit. There are many official and unofficial preparations that these country drug stores use that are simple, easy and economical to prepare. This is true also of the city stores, yet we find that so many of these stores prefer to pay a premium to the manufacturer on peppermint water. They are too busy advertising "Prescriptions a Specialty," to make a pound of ammoniated mercury ointment; a quart of phenobarbital elixir, or to fill a collapsible tube; to use an ointment jar for appearance's sake instead of an ointment tin; time does not seem to permit a little attention to the finished package that leaves the counter of the self-styled prescription expert.

Professional Remuneration.—The price for professional work has long been in the print and in the talk of the average association and among the individuals. We find a group who abhor the fact that we have no regular schedule for professional fees, while the majority seem to be indifferent to the matter. It is to be admitted that there are numerous times when it is impossible to reconcile the charges with what the quality should be. That there is a variance in professional fees in a number of different stores can be attributed to several factors, few, if any, of which would have any economic foundation. The city dweller usually classes the fees of the country drug store with the Jesse James Gang; the city pharmacist frequently bewails the fact that the country drug store is tearing down the professional structure with his disastrously low fees, therefore we find two extremes. Investigation will show they are practiced by the city stores as well as the country stores.

Manifestation of Ability.—From the foregoing it is possible some of you have decided this was an indictment of the retail drug business and that everything was wrong. This, happily, is not the case and can be easily proven by the fact that once or twice in a blue moon we do find a country drug store and what might be termed a country pharmacist who realizes that his professional training was a foundation upon which to build. We further find that he has built wisely because he realizes that the professional end of the business is the keystone to his success. We find this store right up to the minute in equipment, stocks and appearance. We find his finished prescriptions a credit to the profession of Pharmacy instead of the butcher shop. We find that this individual has taken an idea, added an ell, and made an ideal which he has taken as his objective with the hope that he will finally reach his Utopia and that in his travels he will be able to offer an incentive to others to follow.

Conditions like this are rare indeed, comparatively speaking. The fact that they are rare serves to show the possibility for development and also that it will not grow without constant attention to details that the average pharmacists overlook as being insignificant.

Possibilities for Improvement.—Many of the possibilities for improvement of the conditions mentioned lie within the reach of the individual, but these same

individuals must in some manner be awakened. There are a great number in Pharmacy who are not interested in the professional side, and nothing can be done to interest them. There are many who are interested but apparently do not know how to proceed. This group seems to have lost faith in the profession or their ability; maybe both. This group keeps a so-called prescription department for selfish reasons. They prefer to throw a prescription together, extract the money from the customer to keep him from going to an establishment where they do care for prescriptions and make an honest effort to prove it by the work they turn out. In a case of this nature and based on economics taught before the days of "New Dealers," this type store would be better off to discard the Prescription Department and in many instances so would his customers.

It would not be wise to waste time, effort and money trying to show the above-mentioned type stores the possibilities that exist. The second group could in many instances be helped, but the third group, those who are actually interested and who are trying, is the group to help and in so doing the torch you hand to them will help light the way for the others.

When we speak of professional interest in the country drug stores, there are many who immediately think of a prescription when, as a matter of fact, there are quite a number of things that can be included in this category. There are so many preparations that have to be made before a prescription can be turned into a product for consumption, and many of these operations the country drug store can carry out with the time he has at his disposal and with a financial saving, in most instances. To mention a few other factors, there are biologic stains, dyes, ampoules, sterile solutions, the supplying of dispensing physicians and veterinarians. These are often overlooked because of the barrier of hate that we have built up against these practitioners. In short, there are about as many ways and methods of improving our professional business as there are ways and methods of dodging the issue.

Support Necessary for Improvement.—A good bit of this lethargy referred to seems to have become a habit due to the fact that the average country pharmacist has been taught by trade magazines and manufacturers how to cut prices on commercial items and thereby dispose of stagnant merchandise or increase his turnover. But this same individual is absolutely lost in the wilderness when it comes to advertising professionally. Various trade magazines suggest many types of advertising schemes. A few of the manufacturing pharmaceutical houses offer a series of professional ads if the country store will agree to purchase his merchandise exclusively. The few truly professional magazines that exist seldom, if ever, offer a suggestion for professional advertising, much less offer any practical copy. Rather, they seem to lean to the problems related to pure science and extensive research which, it must be admitted, have their place.

Hospital pharmacy in coming out in the open through several of the professional magazines has helped materially the condition of the country store because they have in so many instances dealt with practical issues, and the country pharmacist needs just such encouragement, the type that is plain and smacks with so much sincerity until he knows that it is for his own welfare and not that of some greedy manufacturer or high-powered advertising organization.

There should be an organization to whom the country pharmacist could appeal

for professional advice. It should be so organized that it would coöperate with the colleges of pharmacy, the state boards and the state associations to sponsor professional clinics where matters pertaining to their needs could be practically demonstrated. More actual demonstration and less theory would be mighty helpful. This organization should be in a position to lend assistance with professional advertising and literature pertaining to the profession designed for the physician and the public. They should be in a position to gladly give time and effort to the several U. S. P. and N. F. State Committees to the extent that their work could be more uniform, their services worth more to the physician and the pharmacist, and the cost of such operations more within reason.

CONCLUSIONS.

The organization at present that seems to be best able to handle this situation is the A. PH. A. It has the age, the experience, the organization, the necessary contact with agencies interested in a publication with a reader acceptance. Within the organization there are, or should be, individuals with the intelligence to promote and carry out such work.

The A. PH. A. could easily use the support of more retail pharmacists. It can get them by putting forth efforts that will convince the country pharmacists that they have something besides scientific data to offer them. It would be useless to spend money and time through the JOURNAL OF THE A. PH. A. or other means in trying to sell all the pharmacists in the country or city on the professional end of the retail business because it is extremely doubtful if 25% of the so-called retail drug stores are worth trying to save for Pharmacy. Socialized medicine, if developed in any form, will probably necessitate a change in our present-day methods. The biggest change will be making the change from our old way to a new, and it will be the hardest. In short, many of us will die hard. To say the least, it should be a means whereby Medicine and Pharmacy could and would be more closely welded in their activities, politically and professionally.

The new drug and cosmetic laws, when finally amended and regulations issued, will have a decided tendency to slow down traffic for the many stores who are fighting for turnover. This should open avenues for the professional associations and the professionally-minded pharmacist to build professionally and to make more money in his effort. With the advertising claims of the medicine houses held down to a minimum, who is going to sell the debunked merchandise? And there are many so-called specialty items that should be classed with the so-called patents.

What is going to become of the so-called ethical pharmaceutical manufacturers who load up the country drug store and then load up his only avenue of disposition, the physician? What is this organization doing about it?

The opening exercises of the 110th year of the New York College of Pharmacy, Columbia University, were held in the auditorium on September 27th. Dean Ballard, speaking for the faculty, extended a welcome to the classes, emphasizing that the pharmacy men as students in Columbia not only must uphold the standards of scholarship required of the students in other schools of the University but must also share in the extra collegiate activities. To secure correlation of several courses in the pharmacy program with the corresponding courses in the University it has been necessary to have the opening date coincide with that of the Columbia term.

"DIVIDED WE FALL."*

A Survey of Hospital Pharmacy Associations in the United States.

BY BLOSSOM L. LEHRKE.[1]

After attending the sessions of various state pharmaceutical conventions, the author found that too often papers which took much time and preparation on the part of the authors were accepted by title because of lack of time. Those who did read their papers were listened to eagerly by a few, half-heartedly by most. True, the authors found their articles published later in their respective journals, but how often were they read? Words can be of little value. Only when words precipitate results are they valuable. It is this action which any author values and wants.

The author of this paper deeply appreciates the action received from the questionnaires sent out in gathering data for this paper. Only with such cooperation could this survey of hospital pharmacy associations materialize. At this meeting let there be action and reaction from each hospital pharmacist. Nowhere else will the help we hospital pharmacists need, be received except through the American Pharmaceutical Assocation.

We hospital pharmacists need all the help and coöperation we can secure in order that the professional ethics, ideals and aims of Pharmacy be not in vain. It is at this questionable phase of Pharmacy, that we must find aid from within the ranks of the profession in order that the future of Pharmacy may not be jeopardized.

Pharmacy is a profession which should and must demand the respect of all professions. Why must we constantly be forced to defend ourselves and our profession? Frankly, we should refuse to do so any longer. The time is imminent when we must act and work together in order to erase the clouds that are threatening to obscure the professionalism of Pharmacy, hospital and otherwise.

Because participation leads to understanding, the hospital pharmacists have felt the need of organizing themselves into regional, state and even interstate associations. In fact, hospital pharmacists have made such strides that they are now a sub-section recognized by the American Pharmaceutical Association. This was accomplished at the Dallas meeting of the American Pharmaceutical Association in 1936. The establishment of a sub-section within the section on Practical Pharmacy and Dispensing was brought about through the combined efforts of the members who recognized the importance of hospital pharmacy and hospital pharmacists. We owe much gratitude to Mr. H. A. K. Whitney, Dr. E. F. Kelly, Dr. E. F. Cook, Dr. Robert P. Fischelis and others for their efforts.

We hospital pharmacists have whistled in the dark long enough. Now we want to be heard, to be recognized and to have the respect of allied professions. We demand that state boards of pharmacy be not puppets acting according to the

* Presented before the Sub-Section on Hospital Pharmacy, A. Ph. A., Atlanta meeting, 1939.

[1] Vice-president of Minnesota Hospital Pharmacy Association, University of Minnesota Hospitals, Minneapolis, Minn. Now prescription pharmacist at Medical Arts Pharmacy, Duluth, Minnesota.

pull of political strings but be strong-minded people enforcing all laws already on the statute books which provide for registered pharmacists in hospitals. Why should the public be protected by registered pharmacists and not the patients in the hospitals? We ask their aid in promoting and enforcing the professional aspects of Pharmacy to the nth degree.

In the author's survey of hospital pharmacy associations now existing in the United States, a feeling of isolation predominated. Thus the main purpose of this survey is to cement each group, each association together, enlightening each as to how the other functions, that we be no longer a forgotten department. The author is earnestly striving to arouse each hospital pharmacist to become acutely aware of the importance of working together. That phrase well known in American history, "United we stand, divided we fall," is a statement applicable to hospital pharmacy.

The Hospital Pharmacy Associations now established are: The Western New York Hospital Pharmacy Association at Buffalo, The Cleveland Society of Hospital Pharmacists at Cleveland, The Ohio State Hospital Pharmacists' Association (recently formed), The Nebraska Hospital Pharmacy Association at Lincoln, The Mid-West Hospital Pharmacists' Association including mainly the Iowa and Nebraska groups, Hospital Pharmacy Association of Southern California and the Section of Hospital Pharmacy in San Francisco which are component parts of the Association of Western Hospitals (includes eleven states), The Philadelphia Hospital Pharmacy Association, The Minnesota Hospital Pharmacy Association which is a sub-section of the State Pharmaceutical Association and also a member of the State Hospital Association; The Wisconsin Hospital Pharmacy Association at Milwaukee, and the Tri-State Hospital Assembly including Wisconsin, Illinois and Indiana. This Assembly meets annually in Chicago.

The membership of these associations varies from fourteen to forty-five members. About ten or twelve of these members are members of the AMERICAN PHARMACEUTICAL ASSOCIATION. I urge the affiliation of hospital pharmacists with the AMERICAN PHARMACEUTICAL ASSOCIATION. It will not only give them prestige but will foster the progress of hospital pharmacy.

The problems confronting the hospital pharmacist are many. The main problems are the recognition of the pharmacy as an important unit of the hospital; raising the standards of Pharmacy within hospitals; the promotion and fostering of coöperation between pharmacists in hospitals; the eliminating or reducing to a minimum the purchase of supplies by physicians for dispensing to their private patients; formulating a definite schedule of pricing drugs dispensed in hospital pharmacies, and ever keeping abreast of new products.

The aims of hospital pharmacists have an eye to the future of Pharmacy. They embody a dream that must be realized within a very short time. First and foremost the pharmacist pleads for *recognition of himself and his profession*. A price scale must be evolved that is fair to the best business policies; recognition by colleges of pharmacy whereby they include definite courses in techniques of hospital pharmacy; pharmacy internships in hospitals on a par with internships required by the medical profession. There must be aid from state boards of pharmacy for they possess tools to pave the way to the highest in Pharmacy standards. Recognition from state and national associations of pharmacy are necessary; promotion in salaries for hospital pharmacists that they may enjoy the best standards of living

afforded other professions. All too often the cultural side of a pharmacist's life has had to suffer because of poor salaries.

A gleam of hope may be seen for us when at the recent American Medical Association meeting held in St. Louis, the Council on Medical Education and Hospitals submitted a revised list of "Essentials of a Registered Hospital." Pertinent to Pharmacy was the following: "A qualified person should be placed in charge, preferably a registered pharmacist; whatever arrangement is made, all prescriptions should be filled by a graduate pharmacist." Let us see to it that prescriptions *must* be filled by a registered pharmacist. Hospital pharmacists can accomplish this to the utmost if they will!

PRESENT HOSPITAL PHARMACY ASSOCIATIONS.

Association.	When Formed.	Membership.	Aims.
Philadelphia Hospital Pharmacy Association. President: Mr. Quintus Hoch, Kensington Hospital, Philadelphia, Pa.	September 1938	42 including associate members—24 institutions represented	To more closely unite the hospital pharmacists for the improvement of the methods and practices of the science of hospital pharmacy
Nebraska Hospital Pharmacy Association. (Member of Mid-West Hospital Pharmacy Association including Iowa groups.) President: Miss Edith Blanche Williams, Bryan Memorial Hospital, Lincoln, Nebr.	May 1937	14 active members	1. Internships for pharmacists employed in hospitals 2. To make hospital authorities realize that the pharmacist is a specialist and as such is entitled to recognition, adequate salary and suitable conditions 3. To keep abreast of the new drugs 4. Broaden our views and acquire information to help our patients and doctors
Association of Hospital Pharmacists of the Mid-West. President: Miss Edith Blanche Williams	Recently	Iowa and Nebraska Groups	To promote the service of pharmacy in hospitals. To assure the dispensing of drugs by *registered* pharmacists in hospital clinics and dispensaries
The Cleveland Society of Hospital Pharmacists. President: Mr. Russell Stimson, Huron Road Hospital, Cleveland, Ohio	April 1938	19	To promote hospital pharmaceutical service and thereby help ourselves as well
Ohio State Hospital Pharmacy Association. President: Mr. Roger Lager, University Hospital, Cleveland, Ohio	April 12, 1939	Charter memberships still open as constitution is just being drafted	To promote pharmaceutical service in hospitals
Western New York Hospital Pharmacy Association. President: Mr. Lynn Wiles, Buffalo State Hospital, Buffalo, N. Y.	March 1938	14	Pricing medicines, charging of compensation cases, need to be systematized

Hospital Pharmacy Association at San Francisco, component part of Association of Western Hospitals. President: Mr. B. T. Howiler, Univ. of California Hospital	1938	Not listed	Our purpose and aim is through coöperation, discussions, dissemination of information, attempt to benefit and raise the standards of practice in hospital pharmacy; and thus through administrative cooperation raise pharmacy standards in all hospitals
Hospital Pharmacy Association of Southern California. (Member of Hospital Pharmacists Association of Western Hospitals.) President: Miss Mabel H. Poole, Huntington Memorial Hospital, Pasadena, Calif.	1925	45	Briefly: Mutual advice and support, advancing the standards of pharmacy in hospitals, encouraging the adoption of rational and efficient pharmacy laws and regulations, enlisting the coöperation of other pharmaceutical organizations
Minnesota Hospital Pharmacy Association. President: Miss Hazel Landeen, St. Luke's Hospital, St. Paul, Minn.	February 1936	48	1. To submit at Minnesota State Pharmacy Association a resolution that said body go on record as endorsing minimum standards for a hospital pharmacy outlined by the American College of Surgeons 2. To ask State Board of Pharmacy to investigate Minnesota hospitals to see if they meet said requirements 3. To develop coöperation within pharmaceutical ranks in order to accomplish "A self-sufficient profession."
The Wisconsin Hospital Pharmacy Association. President: Mr. Sol Rankin, Mt. Sinai, Hospital, Milwaukee, Wis.			
Tri-State Hospital Assembly. President: Mr. S. W. Morrison, 1819 W. Polk St., Chicago, Ill. (Meets annually in Chicago)		Illinois, Wisconsin, Indiana	The promotion of professional pharmacy in hospitals

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An attack on cancer, Public Health Enemy Number Two, has been launched along new lines in Pennsylvania. The attack consists of a fact-finding campaign, expected to furnish doctors with strategic information for new and more sure-fire use of the big anti-cancer guns, surgery, X-rays and radium.—*Science News Letter*, Oct. 14, 1939.

COST ASPECTS OF AMPUL MANUFACTURE.*

BY DONALD A. CLARKE.[1]

It is the purpose of this discussion to demonstrate the soundness of being sound, particularly in departmental economy, specifically in the manufacture of ampuls.

The operation of most hospitals, regardless of character, has necessarily reached the status to-day of a business in a true sense of the word. Efficient and economical operation is the constant goal of the administrators. The development and application of a method of accounting by which efficiency and economy may be ascertained in the department of Pharmacy of a hospital is important.

The department of Pharmacy is a true service department, but, simultaneously, represents a potential, if not actual, source of revenue. There are three major units of service offered by most hospital pharmacies, two of which are rendered directly to the public and these two are the revenue producers. The department supplies all nursing floors with the medical material necessary for routine operation as well as the routine care of the patients. Private, semi-private and, on occasions, ward patients are supplied with special medications which are designated as "charge medications." Ambulatory patients are supplied with treatment medications through the medium of an out-patient department. For the latter two mentioned services monetary compensation must be exacted.

Recently one of the Middle Atlantic States apportioned among all of its *privately endowed* hospitals several hundred thousand dollars of the taxpayers' money to help these hospitals clear their operating deficit for the fiscal year 1939. It is the opinion of the author and others that whenever any hospital department deals directly with the public and charges for the service rendered, the charge should be so adjusted that at least the actual cost would be represented by the reimbursement. If so, the particular department concerned would not be adding to the deficit burden of the entire institution and the cost for these direct-to-the-public-services would be obtained from the taxpayers who are immediately benefited. Unfortunately this plan cannot be extended as far as to cover patient-day costs of a hospitalized patient, but it can be applied to departments of Pharmacy where the costs of services rendered are decidedly lower.

Hospital pharmacists, as a rule, have been grossly indifferent to actual cost when setting prices for the sale of medical supplies to the public. These prices are set with little or no concern for direct material costs let alone the multitude of indirect costs which arise from the operation of a pharmacy in a hospital. It becomes necessary, therefore, to reduce every unit of medical supplies dispensed as a service to nursing floors, in-patients, or out-patients to an actual cost figure, which figure must include both direct and indirect costs. By so doing, the department is immediately placed on a potentially sound accounting and administrative basis.

The formula costs, in the large variety of manufactured products in a pharmacy, change because of a fluctuating market for basic drugs. Maintaining

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* Presented before the Sub-Section on Hospital Pharmacy, A. PH. A., Atlanta meeting, 1939.

[1] Chief Pharmacist, The New York Hospital, New York City.

actual costs under these conditions would be too great an accounting burden although the accurate method. To eliminate the necessity of changing costs with each market fluctuation a system of "standard costs" is advocated, which applied to materials is as follows.

Applying these costs to the formulas for the preparation of finished products will give the standard material costs upon which are based the final values of all units of material dispensed. Differences between the predetermined values and the actual cost will be accumulated in a variation account until the end of the period of operation. At this time, the difference, which may be a surplus or deficit, will be spread over the services supplied by the pharmacy. Incidentally, this difference and its character will gage accurately the market trend—whether up or down. It will also indicate whether or not good judgment has been used by the individual responsible for purchasing.

Consider some of the "intelligent" uses to which the system of standard costs may be put: The value of all materials on hand at any one time may be estimated with a great degree of accuracy. This gives all the desirable features derived from a perpetual inventory. The department of Pharmacy can definitely operate its two revenue-producing services so that at least no loss is experienced.

By using standard cost prices to price the requisitions from the nursing floors for supplies the hospital accounting department may determine the exact cost of medical supplies used on the nursing floors and may use this figure for building up the patient-day costs. Thus by means of standard costs the department of Pharmacy can ascertain that its two revenue producing units are paying their own way and can turn over to another department all the figures necessary from the pharmacy to make income from hospitalized patients cover the cost of patient days. In this way the department of Pharmacy cancels its financial obligations to its institution satisfactorily.

Standard costs present figures, devoid of all guesswork, which are either in favor of or not in favor of a program of manufacturing. If standard costs are favorable as compared with market costs and continue favorable, as the manufacturing program progresses, the pharmacist has a strong platform upon which to stand in proving to his institution the value of the functions of his department. Standard costs, simultaneously, eliminate any false conception of economy. Many hospital pharmacists perform their duties with an inflated conception of the economy effected.

No one ever economized by lowering quality. Consequently, we must maintain quality in our production. In so doing we are actually and necessarily competing with manufacturers of repute whose products must be beyond question in quality. The ampul we manufacture must be equal or superior to a similar ampul which might be offered the profession by one of these manufacturers. Hospital pharmacy cannot allow itself to descend to the level where ampuls are manufactured in any fashion. There is far more to be considered in the manufacture of an ampul than just the material costs.

Primarily, it is necessary to have the proper type of laboratory, completely equipped with all the essential apparatus. The best materials available must be used and the operator of the laboratory must be skilled in his work and thoroughly grounded in his knowledge of the chemicals used and their peculiarities under

varying conditions. The moment that an ampul laboratory starts to function as a unit of the pharmacy a great number of indirect services are brought into play. Underlying all this must be a continued, never-ceasing, program of research or practical study to constantly improve upon original techniques.

The laboratory must be isolated from all other activities than those directly concerned with sterile or aseptic technique. The space employed must actually be walled off and air-tight to prevent as completely as possible contamination of solutions with pyrogenous material. To allow ventilation and to ascertain that the air supplied is *clean* an intake ventilator is required. The usual exhaust ventilation shaft must be absent. Into the mouth of the ventilator is built a small intake fan backed by a "spun-glass" filter which cleans the air. When the fan is in operation, the laboratory is assured of a constant supply of clean air for it builds up a sufficient air pressure within the room to keep the flow passing from inside out through any tiny crevices. Windows should be weather-stripped and permanently sealed. If the windows are exterior, it may be more desirable to remove a pane of glass and build the intake fan with its filter into this space. The laboratory need not be large—a space fifteen feet square is more than ample. It may be constructed readily by using a corner section of a larger room and walling it off with two walls constructed of large squares of window glass set in partition casements. The laboratory should be supplied with water, waste lines, a sink, electric, gas, air and vacuum outlets if all of these are available. Tanks of compressed air or oxygen may be used to substitute for air lines. Vacuum may be substituted by use of the faucet aspirator pump.

The equipment of major importance includes: a small autoclave or a good pressure cooker, a hot-air oven, an electrically heated Pyrex glass water still of at least 2000 cc. capacity, a small incubator, a gas plate, a blow torch, a laboratory table and a stool. Many other pieces of equipment, especially glassware, which are too numerous to mention here are incidental to ampul manufacture.

Selection of the ampul container to be used is an important detail. The best ampul container available should be used. Select a container composed of a glass which will not when exposed to sterilization or under normal but lengthy storage conditions liberate sufficient free alkali to cause difficulty in the finished ampul. Some ampul solutions can be buffered against the action of alkaline glass; many, however, cannot. Select also a strain-free glass since breakage while sterilizing is a costly experience. From laboratory performance and a review of published reports on ampul glass, we find that certain domestic ampul containers are now superior to the foreign ampuls that have been imported.

In preference to a paper label, an etched or baked pigment label is necessary when the ampul is to be immersed in a sterilizing storage fluid such as 70% alcohol for a period of time before use. An acacia-base glue may be used on paper labels with fair security under these conditions. However, for complete assurance against loss of identifying labels an acid, alkali, alcohol resistant, baked pigment label will prove most successful.

Water to be used as the solvent for an ampul solution must be absolutely pure for reasons of both safety and stability of the solution. The requirements of the National Formulary for "Ampul Water" leave nothing to be desired and should

be adhered to. The distillation of ampul water of these standards is accomplished by the Pyrex glass still mentioned under the discussion of equipment.

When it appears necessary to use a buffer solution in preparing the ampul solution, agents should be used which are both physiologically and chemically compatible. The buffering solution schedule of Clark and Lubs has proved quite generally applicable although not so in every case. It may become necessary to develop a buffering or stabilizing agent for difficult cases.

The grade of chemical to be used in the ampul solution can only be determined by experience. In many instances it will be found preferable to use chemicals which are graded above the U. S. P. or N. F. standards.

The ampul container, the label, the buffer solution and the active chemical or chemicals used represent the material costs in the manufacture of an ampul which are usually accepted as the basis for determining the individual cost of a finished ampul, and the economy effected. However, to arrive at the true cost of the finished ampul it becomes necessary to develop the "standard cost" of the unit. Let us, therefore, analyze the costs over and above the material costs, which are commonly termed indirect costs which must be determined to develop the standard cost and which cover services rendered to the pharmacy by other departments of the hospital.

The most important indirect cost is that of labor. Experience shows that to maintain a record of the time each employee spends in making each preparation is costly and the following simpler method is suggested. Each employee during the day will spend some of his time in services to the hospital nursing floors, some for private and semi-private patients, and some for ambulatory patients. If the amount of time spent in each of these three units can be accumulated, expressing this in dollars and cents, a labor distribution can be established as well as the percentage relationship between labor cost so arrived at and the material cost by services. By applying this percentage to the material value of every item dispensed, a cost for material and labor can be arrived at.

Further indirect costs include such items as heat, light, power, depreciation (replacement of equipment), laundry, and so forth.

The final indirect cost of the group is represented by the apportionment of the costs of operating all the administrative departments which function in behalf of the pharmacy such as the accounting department, the purchasing department, and so forth.

For the purpose of this paper a study has been conducted in New York of the 1938 department of Pharmacy figures for six different New York City, privately endowed, hospitals ranging in bed capacity from 300 to 900. The study was made to determine a relationship of indirect costs to labor costs. Interestingly enough all six institutions demonstrated a fairly comparable relationship. An average of 32% of the money spent for labor gives a figure which represents all other indirect costs for the combined institutions.

The application of the described standard costs system of accounting at The New York Hospital has shown that labor cost represents approximately 30% of material costs on every item handled. We therefore have indirect costs reduced to two percentage figures which may be considered fairly average. By applying these two overhead percentages to a material cost of $1.00, the standard cost is

shown to be $1.40. As a concrete example, the manufacture of a thousand 1-cc. ampuls of a 2% solution of Procain Hydrochloride may be considered.

In the manufacture of these Procain ampuls will be used one thousand of the best ampul containers available, 1100 cc. of solution containing 22 Gm. of a Procain Hydrochloride and one thousand paper labels. The material cost for this operation will be approximately $24.50. These might be bought on the open market for $40.00. Without giving thought to labor and indirect costs there is an apparent economy of $15.50.

However, applying the overhead figures presented above the standard cost on these ampuls would be $34.20 a thousand. The *actual* economy is $5.80 or about three-fifths of a cent per ampul. Furthermore out of this saving would have to come any cost for materials used for research and any breakage. These two items can be determined only after a batch of ampuls has been manufactured. The resultant figure must be added to the standard cost.

IN SUMMATION.

In presenting this paper, I have attempted to point out how necessary it is that Hospital Pharmacy firmly establish itself through a system of accounting which is simple, efficient and, above all, applicable. I have reviewed the development of an ampul manufacturing program to demonstrate why all of the components of the described system of accounting apply to this particular phase of Hospital Pharmacy. And, finally, the components of the accounting system have been brought together and applied to a manufactured ampul to demonstrate to what extent the resultant product is affected by indirect cost factors.

This has been done with the one hope that, if you are anticipating the manufacture of ampuls or the inauguration of any new manufacturing procedure, you will not go blindly ahead believing implicitly that you are a "Midas" and that everything you manufacture immediately shows an inconceivably wide margin of economy; that you will find in this analysis the incentive to bring your own activities down to facts and figures for your good in particular and the good of Hospital Pharmacy in general.

One final thought. Do not be discouraged if the economy you might anticipate is not apparent. Professionally, we are pharmacists and as pharmacists it is our privilege and duty to pursue the opportunities granted us as far as it is economically feasible.

A DAY OF THANKSGIVING.

Thanksgiving Day is the most truly American as it is the oldest of all our national holidays, and our celebration of it will not be complete if we forget to give thanks for American ideals as well as for American prosperity. Unique among the nations of the earth, this nation will this year rededicate itself to that Power which guides the destiny of man, and give thanks for the precious things the year has brought. That such a day should have been set aside for national observance was most appropriate. Let us not forget the inspiration which was its inception.

NEW LABELS VS. OLD LABELS.*

BY SAMUEL SHKOLNIK.[1]

As early as 1849, Congress sought to prevent importation of adulterated drugs into this country. This effort was intensified in 1852, the year of the organization of the AMERICAN PHARMACEUTICAL ASSOCIATION. Indeed, one of the expressed objects of the ASSOCIATION was to assist the United States Government in its undertaking in that field. It was not, however, until 1906 that Federal legislation of a general nature was enacted in an attempt to free the channels of interstate commerce from adulterated and misbranded drugs. In that year, the "old" Food and Drugs Act was enacted into law. While that law accomplished a great deal, measured by the then existing evils in the sale and distribution of drugs and medicines which had been curbed thereby, it was woefully inadequate for the purpose intended when measured by the abuses which subsequently developed or were continued thereunder. The new Federal Food, Drug and Cosmetic Act of 1938 constitutes a radical departure of the Act of 1906 and is intended to stamp out the many abuses which had been in evidence during the 32 years of the operation of the old law. While the law also prohibits adulteration and regulates introduction of new drugs, it is popularly considered by retailers mainly as a "labeling law," that is, the provisions with regard to labeling seem to be the paramount topic of discussion. It steals the show, so to speak. "Have you seen the new labels?" or "what about the new labels?" and similar expressions seem to typify retailers' current concern in and discussion of the Act—hence, the title of this paper "New Labels *vs.* Old Labels."

Rather than set out in detail all of the labeling requirements under the law, let us discuss a few specific practical features of it of interest to retailers. To begin with, a medicine for human medication containing any of certain enumerated narcotic or hypnotic substances, like codeine or barbituric acid, for example, must be labeled so as to indicate the presence of such substances both qualitatively and quantitatively with the added legend "Warning—may be habit-forming." You can readily appreciate that such information on the label will in many instances seriously affect the volume of sales of preparations containing such narcotic or hypnotic ingredients—the warning phrase acting as a scarecrow. The practical result of it may be that the customer will either ignore it, or shift to another patent medicine without such warning phrase on the label or ask the pharmacist for an extemporaneous preparation of his own, or abandon entirely self-medication in favor of a physician's diagnosis and prescribed individual medication, the latter two results being decidedly advantageous to the profession.

Secondly, a non-official medicine containing two or more active ingredients must be labeled so as to indicate the presence of each active ingredient at least qualitatively, and in the case of certain enumerated ingredients, like alcohol and bromides, for example, quantitatively as well. Here again the practical result of

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* Presented before the Section on Pharmaceutical Economics, A. PH. A., Atlanta meeting, 1939.

[1] Instructor in Business Law, University of Illinois, College of Pharmacy; and Legal Counsel, Illinois Pharmaceutical Association.

that may be the same as in the case of the patent medicines containing a narcotic or hypnotic ingredient; that is, the customer will either ignore it, or shift to another preparation which does not contain the ingredient deemed objectionable or ask the pharmacist to recommend an extemporaneous preparation of his own, or abandon entirely self-medication in favor of a physician's diagnosis and prescribed medication, the latter two results—as already stated—being decidedly advantageous to the profession. In other words, all of this professional information on the label at least in the case of the masses of scientifically uninformed buyers of self medications, and those are by far in the majority, will serve to initiate a conversation or discussion between the customer and the pharmacist regarding a given product which, in many instances, will undoubtedly lead to either of the two aforementioned favorable results from the standpoint of the pharmacist, namely, an acceptance of the recommended extemporaneous preparation of the pharmacist, or a shift to a physician's diagnosis and prescribed medicine.

Another so-called new label problem of particular concern to the retail pharmacist is the "repacking" provision of the misbranding regulations. Pharmacists frequently buy from manufacturers located in different states familiar bulk goods, like Elixir of Terpin Hydrate with Codeine, Compound Syrup of Cocillana or Cheracol, for example, in gallon lots and resell it on call over the counter (as well as on prescriptions, of course) in small quantities. The manufacturer may in such cases omit from the label on the gallon bottle the directions for use by placing thereon the statement "Caution: to be used only by or on the prescription of a physician." The pharmacist, however, in reselling such product on call over the counter, even though such sale is intra-state only, so long as the purchase of the gallon lot was made across the state line, must label the two- or three-ounce bottle which he sells, in full compliance with all of the provisions of the Federal law, including name, formula disclosure, warning against habit-forming, directions for use, etc., the same as the manufacturer would have had to label it had he shipped it to the customer in a two- or three-ounce bottle directly from his plant located in a different state. Of course, if the gallon goods are purchased from a local manufacturer within the state, no interstate commerce is involved at any stage of the transaction and the labeling requirements of the Federal law are not applicable.

Lastly, the labeling requirements of the law in the case of medicines dispensed on physicians' prescriptions, are not as favorable as many pharmacists feel they ought to be. While an attempt has been made to create an exemption in such cases, the provision is so worded as to make the exemption meaningless in the case of "refillable" prescriptions. For example, a prescription calling for 3 fluidounces of Elixir of Terpin Hydrate with Codeine, which is generally and legally considered a refillable prescription, would (if the bulk Elixir were purchased in interstate commerce or if the prescription were to be shipped in interstate commerce) have to be labeled so as to meet all of the detailed labeling requirements of the Federal law referred to above, including the phrase, "Warning—may be habit-forming," in addition to the usual and customary prescription labeling. While it is the writer's opinion that such result was never intended, nor necessary, nevertheless the provision of the law is as indicated above; and it is hoped that the administration will place a saner interpretation on it than the language permits.

Retailers have repeatedly asked the question "What about old label mer-

chandise remaining on our shelves after the law takes effect?" *Drug Topics* has already very effectively answered that question with a dramatic picture on the cover of a recent issue in which retailers were appeased and advised not to worry about the G-man getting after them. It should be added that reputable manufacturers will undoubtedly work out some practical plan in the handling of their old label merchandise, particularly after their new package has been advertised and introduced to the public, in order to avoid unnecessary explanation and possible sales resistance at the drug counter. Of course, some difficulty may be encountered with the adjustment of old label merchandise of questionable manufacturers, and retailers should guard themselves against it in advance. But, on the whole, the problem of old label merchandise remaining on the retailers' shelves after the law takes effect, could hardly be considered as a serious one.

In conclusion, we should not be blinded into the belief that the new law will prove a panacea to all the ills which were prevalent under the old act. Far from it. It must be borne in mind that the "misbranding" section, as drastic and as all-inclusive and sweeping as some of us may think it is, is nothing more than a "labeling statute" covering only information which may or may not, or must, be given on the label and accompanying literature in the sale of foods, drugs, devices and cosmetics, and even then only in the case of such as are shipped or introduced for shipment in interstate commerce. The law does not cover the manufacturing or production angle of such commodities except indirectly in the case of "new drugs" within the meaning of the Act. In other words, it is not what a manufacturer puts into the bottle, so long as it is not adulterated, but what he says about it in the labeling on and accompanying it, that determines whether or not he committed an unlawful act under the law. The public first commences to enjoy the benefits of its provisions only after the product had been manufactured, labeled, shipped in interstate commerce, seized, analyzed, found to be either adulterated or misbranded, or both, and the enforcement machinery had been set in action and successfully concluded—but not before. Until all of these things had taken place—and in the case of many products it may either never take place or only after the wrong had been committed—the public remains unprotected under this law.

The writer is not prepared to say whether Government control and regulation of the manufacturing or production of foods, drugs, devices and cosmetics, as in the case of production and bottling of "bonded whiskeys," for example, is legally possible or generally desirable or necessary. That is a matter which requires serious and careful consideration as well as a study of a number of factors in the light of existing laws, experiences, necessities and circumstances. From an abstract viewpoint, however, it would appear that in order to afford the maximum protection to the public—particularly the masses of unintelligent buyers of foods, drugs, devices and cosmetics—authoritative regulation and control at the point of manufacture or production of these products is equally, if not more, essential than that provided under the Act.

MAIMONIDES.

Maimonides was born March 30, 1135, and died December 13, 1204. Though he lived and worked in the twelfth century he typified the highest qualities of medical and pharmaceutical ethics. His devotion to his calling was expressed in a classic prayer, which has been handed down to us. This prayer, in two colors, for framing, is for sale by the JOURNAL OF THE A. PH. A., at 25¢ a copy.

1939 PRESCRIPTION SURVEY.*

BY J. H. GOODNESS.[1]

At the very outset of this report I wish to thank the secretaries of both the State Boards and the State Pharmaceutical Associations for contacting the druggists in their states and requesting reports upon which this survey is based. And it goes without saying that this report is made possible only because of the patient effort of the retail pharmacists who without desiring credit or recognition kept accurate and detailed records of their prescription work for a full month. It is hoped that some benefit, however slight, may accrue to all pharmacists as a result of their efforts.

This survey was undertaken in an attempt to answer two questions, namely: Is the Nature of Prescriptions Changing? and How Are Prescriptions Distributed through Time and Customers?

In searching for the answers to these two questions several incidental questions were answered. The findings in each case are based upon reports for new prescriptions filled during the month of June.

While it is clear that June is a "slow" prescription month, most of the findings should not be materially affected by the fact that this survey was made during the summer. Certainly the study of prescription ingredients and their percentages should not be very different, if at all, were the survey conducted during the winter months. The only difference, it would seem, would be that there would be a greater number of prescriptions to analyze.

The survey includes both narcotic and non-narcotic prescriptions. It does not include refills.

Collection of Data.—To collect the information upon which this survey is based, the author mailed a number of copies of two different report sheets to the above-mentioned officials who in turn distributed them to local pharmacists.

The first sheet bore the caption "Is the Nature of Prescriptions Changing? (New precriptions.)" The sheet consisted of seven columns headed as follows: 1, Date; 2, One-ingredient Prescriptions, Nonproprietary; 3, One-ingredient Prescriptions, Proprietary; 4, Several-ingredient Prescriptions, All Nonproprietary; 5, Several-ingredient Prescriptions, All Proprietary; 6, Several-ingredient Prescriptions, Mixture; 7, Total Prescriptions.

A proprietary was defined as an "ingredient called for by brand or trade name." Provision was made for remarks and identification of store.

The second sheet bore the caption "How Many Prescriptions per Customer? (New prescriptions.)" This sheet contained five columns headed as follows: 1, Date; 2, One Prescription per Customer; 3, Two Prescriptions per Customer; 4, More Than Two Prescriptions per Customer; 5, Total Prescriptions for the Day.

More than 80 druggists from 28 states mailed in either one or both of these reports. The reports from 76 stores arrived before calculations had begun. A few of the conclusions of the survey follow.

Sole Proprietary Prescriptions.—It will be remembered that the "St. Louis" or National Drug Store Survey conducted in 1930–1931, during which the prescription business in four professional pharmacies was very thoroughly analyzed, revealed that "Approximately 25%...of the prescriptions...called exclusively for specialties."

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* Presented before the Section on Pharmaceutical Economics, A. PH. A., Atlanta meeting, 1939.

[1] Professor of Business Administration, Massachusetts College of Pharmacy, Boston.

Specifically, this meant that a study of 1000 prescriptions compounded during 1910 revealed that 23.6% were for "specialties," or proprietaries. No classification was made for narcotics and non-narcotics because the Federal Narcotic Act was not then existent.

In 1920 the analysis of 1000 prescriptions from the same store revealed that 23.1% were for "specialties" or proprietaries. Divided into narcotics and non-narcotics, the percentages for specialties or proprietaries were: narcotics 9.3%, non-narcotics 25.5%.

In 1930 an analysis of 8670 prescriptions from two stores showed that 22.81% were for specialties. This figure included narcotic and non-narcotic specialties.

Summarizing, we find that specialties or proprietaries in 1910 were 23.6%, in 1920 they had decreased to 23.1%, and in 1930 were 22.81%: thus, the "approximately 25%."

In November 1937, an ingredients analysis of 535 non-narcotic prescriptions as compounded by a Greater Boston professional pharmacist revealed[1] that specialty or proprietary prescriptions totaled 46.5% of those compounded. This present survey was undertaken to see whether the national average had increased to this high point.

The 1939 condition as revealed by reports of 70 stores located in 27 states is as follows: Of the 24,259 prescriptions compounded 8634 or 35.59% were for a sole proprietary ingredient; 1022 or 4.21% were for mixtures of proprietaries only, yielding a total of 9656 or 39.80% of the prescriptions which called solely for proprietaries. The conclusion is, therefore, that prescriptions calling solely for proprietary ingredients have increased from a 20-year constant of 25% to 40%—an increase of 60% in less than a decade.

This percentage of proprietary prescriptions varied from state to state, and in Indiana, one of the states well represented, reached a total of 44.57%. For other state averages see Chart A.

The comments of druggists on this part of the survey reveal a growing tendency of physicians to prescribe for proprietaries alone. That the number was not higher in at least three of the reports was attributed to the fact that a great many prescriptions were written for "welfare" patients whose physicians were under instructions to prescribe official or non-proprietary preparations where possible and in this way keep down the cost. There is no doubt but that many other stores were operating under similar conditions but did not mention the fact in the remarks.

One druggist revealed that his rather small percentage of proprietary prescriptions was due to the fact that clinic physicians whose prescriptions he filled favored the official or non-proprietary type of medication. Such cases of decreased proprietary prescriptions are either laudable or unavoidable, but they were not the only comments listed.

A Virginia druggist estimated that his "proprietary prescription" total would have been 15% higher if customers did not turn prescription business into over-the-counter sales by orally ordering the medicines that had been prescribed by their easily read English trade names. Several druggists explained that the physicians in their neighborhoods "dispensed" (dealing with proprietary medications almost exclusively) and that at least one physician either furnished or sold to patients the large detail samples furnished him by manufacturers, all of which tended to decrease prescription business, especially in this class of medication.

Chart A reveals the percentages of proprietary prescriptions in Massachusetts, Indiana, Wisconsin, Maine, New York and Maryland, each of which had four or more reporting stores.

Prescriptions with Proprietaries.—In addition to prescriptions calling for proprietaries solely, proprietaries were also found in the "mixture" prescriptions. Occasionally these mixtures are almost exclusively proprietary. They were placed in the "mixture" class merely because they contained a diluting non-proprietary vehicle.

The St. Louis Survey reported that this type of prescription constituted 23.3% of total prescriptions in 1910, 24.9% during 1920, and in 1930 it was 23.5%.

In 1937 the Massachusetts College of Pharmacy Prescription Survey[2] revealed this class to be only 12.33% of the total prescriptions compounded. This present survey shows that the United States average is 12.32%. If we combine the sole proprietary prescriptions with the mixture prescriptions, we find that prescriptions containing proprietaries were 46.9% of the total in 1910, 48% in the year 1920, 46.3% in 1930, 58.87% in 1937, and this survey reveals the national per cent to be 52.12%.

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[1] "A Survey of Proprietaries in Prescriptions," JOUR. A. PH. A. (January 1939), page 44.

[2] See note (1).

It can safely be said that more than one-half of the prescriptions compounded to-day contain some or only proprietary ingredients.

Miscellaneous.—The 70 drug stores whose reports constituted the basis of the ingredients study ranged in size from 30 prescriptions for the month to 1686 prescriptions, with a median value of 250 prescriptions. Only three stores reported more than 1000 prescriptions during the month.

The distribution of the reporting drug stores by the size of their prescription business is as follows:

Less than 100 Prescriptions	12
100 to 199 Prescriptions	14
200 to 299 Prescriptions	16
300 to 399 Prescriptions	10
400 to 499 Prescriptions	1
500 to 599 Prescriptions	2
600 to 699 Prescriptions	4
700 to 799 Prescriptions	3
800 to 899 Prescriptions	4
900 to 999 Prescriptions	1
1200 to 1299 Prescriptions	2
1600 to 1699 Prescriptions	1

The reports were distributed through the states as follows: Arkansas 3, California 1, Colorado 1, Connecticut 1, Indiana 7, Florida 2, Kansas 1, Kentucky 1, Maine 5, Maryland 4, Massachusetts 11, Michigan 2, Nebraska 1, New Hampshire 2, New Jersey 1, New Mexico 2, New York 5, North Carolina 1, North Dakota 3, Ohio 1, Pennsylvania 2, Tennessee 1, Vermont 1, Virginia 1, Washington 2, Wisconsin 7, Wyoming 1.

The average store according to the ingredient sheets in this survey filled 11.55 prescriptions a day, 80.85 a week, and 346.55 a month.

Of the states having four or more reporting stores, New York had the lowest averages: 4.26 a day, 29.82 a week, 127.80 a month. The Maryland averages were raised considerably because of the presence of one of the four stores which compounded 1201 prescriptions during the month. Maryland's averages were 16.39 a day, 114.74 a week, and 491.75 a month. The monthly average is more than 200 prescriptions above the median value.

These daily-weekly-monthly averages differ slightly between the ingredients-sheet study (Chart A) and the prescription-distribution-sheets findings (Chart B), because the number of stores reporting in each section is not the same, and where they are the same in number differ in identity. For example, Maine reports 5 stores in each section, but only 3 of the stores are coexisting in both lists. The remaining two stores are different and have a difference of over 700 prescriptions. This difference in number of prescriptions causes slightly more than a 50% difference in daily-weekly-monthly averages: for example, the daily average for Maine is 8.07 prescriptions in one study and 12.14 in the other. For this reason, in addition to the fact that but few stores from each state reporting are represented, the states' daily-weekly-monthly averages are not too reliable.

For comparison, Doctor Whitney's very recent figures for Michigan, based upon an annual study of very many, if not all stores in the state, showed an average of 4.5 prescriptions a day. Two Michigan stores reporting here showed an average of 16.3 prescriptions a day. In New Jersey, Doctor Fischelis, reporting on the annual conditions of Pharmacy in his state for 1936 showed an average of 9.2 prescriptions daily per store. The New Jersey average in this study, based upon but one report, is 3.4 prescriptions. The conclusion is, then, that the national average for daily prescriptions is perhaps somewhat high for all stores. This discreditment of the daily-weekly-monthly averages should not, however, seriously affect the *percentages* for 1-, 2-, 3-, and 4-prescription customers in a state, nor the distribution of these customers in time in the average pharmacy. It is as a check on these figures that the daily averages were figured.

That prescription compounding is tending toward simplification can be easily comprehended when we see that the present national average shows that 62.97% of prescriptions were of the one-ingredient type. A one-ingredient prescription usually means that the compounding

duties consist of either changing bottles or labels, or both. Bench work is reduced to a minimum in this class of prescriptions. Occasionally, however, a one-ingredient prescription may call for compounding, as for example, in the case of a prescription calling for Basham's Mixture, Solution of Potassium Citrate or like preparations that should be freshly prepared.

Again comparing the findings with the National Drug Store Survey of 1930–31, the 62.97% of single-ingredient prescriptions for 1939 is quite an increase over the 39.7% for 1910, the 43.7% for 1920 and 41.4% for 1930. The three last-named figures are each based upon a thousand prescriptions (narcotic and non-narcotic) taken from one store for each of the years represented.

The several-ingredient prescriptions in 1939 constituted only 37.03% of the total—almost a reversal of conditions as depicted by the 1930–1931 investigation.

The reports in this survey made no provision for counting separate ingredients but that the average number of ingredients per prescription is decreasing is shown by the comparison of 2.2, 2.3 and 2.1 ingredients as reported for 1910, 1920, 1930 in the National Drug Store Survey and the 1.77 ingredients revealed by the Massachusetts College of Pharmacy 1937 Prescription Survey.[1] No study of the number of ingredients in the several-ingredient prescriptions was made for 1939.

Daily Distribution.—A graph (Chart C) shows that Saturday is the best prescription day with Monday ranking a close second. Sunday is the poorest day of the week averaging less than 50% of the Saturday total, and Wednesday is average, that is, the Wednesday totals are closer to the National Daily average from week to week, even though Thursday has a closer numerical average. The beginning of the month shows a slightly less number of prescriptions for the first three days than the last three days of the month, but this cannot be taken as a conclusive tendency until a study for several months is undertaken.

The daily distribution graph is based upon 54 of the 70 ingredient-sheet reports summarized in Chart A. Five of the 70 reports were from stores that closed Sundays and 11 reports furnished only monthly summaries; thus, 16 of the 70 reports were not used. The 54 stores that were used came from 24 states. The three missing states are Michigan, New Jersey, and Pennsylvania; all other states as found in the ingredients study are represented.

Prescription Distribution.—The second report sheet which druggists were asked to fill out dealt with the distribution of prescriptions among customers and in time. Sixty-eight stores in 27 states filed such reports. The states are the same as those already listed under ingredients study except that Tennessee is missing and in its place we have West Virginia. All 68 stores are not included in the 70 stores of Chart A. Since this report classifies customers into 1-, 2-, and more-than-two-prescription customers it was possible to divide the customers into groups; namely, those presenting one prescription, two prescriptions, three prescriptions, and four prescriptions. The last two classifications were possible because of their rarity in the last column of the sheet.

It will be noted that not a single customer presented more than 4 prescriptions throughout the period of the survey. It is not to be assumed that the several prescriptions presented by any one customer were for the same patient.

One-Prescription Customers.—One-prescription customers were by far the most numerous class. The national average showed that 83.76% of the prescription customers were in this group. They were responsible for 70.48% of the total prescriptions compounded and, distributed in time, averaged 8.17 such customers per day per store. One-prescription customers in no case fell below 80% in the states summarized in Chart B—those states having four or more reporting stores. The highest average was 91.31% for Maryland.

Among customers their frequency was one in 1.18, or in more understandable terms and in round figures 6 out of every 7 customers presented one prescription for compounding.

Multiple-Prescription Customers.—Customers presenting more than one prescription are, of course, less frequent. Dealing in the order (*a*) two-prescription customers, (*b*) three-prescription customers, (*c*) four-prescription customers we find that the national averages are 13.76%, 2.36%, 0.11%. They were, respectively, responsible for 23.16%, 5.95%, and .38% of the total prescriptions compounded.

The daily frequency in the average store was 1.34 for the two-prescription customers or 4 such customers in 3 days; 0.23 of three-prescription customers or 3 in 13 days; and 0.011 of four-prescription customers or 1 in 89 days.

[1] See note (1), page 693.

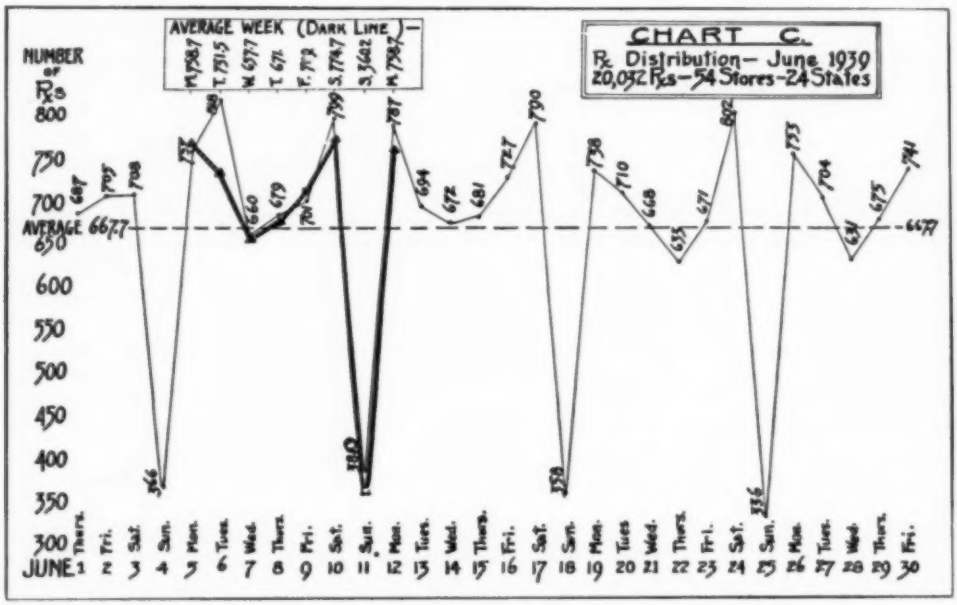
Their frequency among prescription customers was 1 in every 7.26 for two-prescription customers or 4 such customers in every 29 presenting prescriptions; 1 in every 42.3 of the three-prescription customers or 3 three-prescription customers in every 127; and the four-prescription customers were found in the frequency of 1 in every 865.

Percentages and frequencies of these multiple-prescription customers for Massachusetts, Indiana, Wisconsin, Maine, Maryland and New York can be found in Chart B.

CONCLUSION.

Summarizing the conclusions already listed, it can be said that the nature of prescriptions is changing, and the change is toward the simplification of ingredients (increase of one-ingredient prescriptions) and away from official and nonproprietary preparations.

The distribution summaries substantiated the conclusion known in a general way, that one-prescription customers constitute not less than four-fifths of those who seek professional service of the pharmacists.



What practical use can be made of these conclusions will, of course, differ with the nature of the business, the individual and the locality, or combinations of these elements. While they may mean one thing to the manufacturer of proprietaries, to the retail pharmacists, especially to those who have been in business for the last ten years or more, they mean either a change of buying policy to conform with the present conditions or the commencement of counteracting forces.

It is well understood that the profit margin is much smaller on proprietary prescriptions than on official preparations. Also that the cost to the patient is less for the latter class of medication.

Except for the manufacture of those proprietaries, the creation of which demands facilities far beyond those possessed by the retail pharmacists, an increase in proprietary prescriptions has the tendency of decreasing the professional aspects of retail work.

Those pharmacists who have been successful in their prescription departments have either specialized in this work, detailed their local physicians, manufactured as "own-brand" the simpler forms of prescription specialties, or engaged in combinations of these activities.

Every retail pharmacist must remember that both income from the prescription department, as well as income from every other department, either directly or indirectly is geared to professionalism.

CHART A.

	Number of States Reporting.	Number of Stores Reporting.	Total Number of R's.	Lowest Number of R's	Median Number of R's.	Highest Number of R's.	Number of R's in Average Store. Per Month.	Per Week.	Per Day.	One-ingredient Nonproprietary R's. Number.	Per Cent.
United States	27	70	24,259	30	250.0	1686	346.55	80.85	11.55	6642	27.37
New England	5	20	5479	49	221.5	686	273.95	63.91	9.13	1611	29.40
(No R. I. reports)											
Massachusetts*	1	11	2411	60	192.0	686	219.18	51.14	7.30	596	24.72
Indiana	1	7	2923	110	353.0	853	417.57	97.43	13.91	867	29.66
Wisconsin	1	7	1866	42	209.0	824	266.57	62.19	8.88	571	30.62
Maine	1	5	1822	137	362.0	638	364.40	85.02	12.14	536	29.41
New York	1	5	639	63	101.0	205	127.80	29.82	4.26	222	34.74
Maryland	1	4	1967	174	296.0	1201	491.75	114.74	16.39	415	21.09

* Only states with four or more reporting drug stores are here analyzed.

CHART A (*Continued*).

	Several-ingredient Nonproprietary R's. Number.	Per Cent.	Total Nonproprietary R's. Number.	Per Cent.	One-ingredient Proprietary R's. Number.	Per Cent.	Several-ingredient Proprietary R's. Number.	Per Cent.	Total of Solely Proprietary R's. Number.	Per Cent.	Several-ingredient Mixture R's. Number	Per Cent.
United States	4972	20.49	11,614	47.87	8634	35.59	1022	4.21	9656	39.80	2989	12.32
New England	1294	23.61	2905	53.02	1888	34.45	157	2.86	2045	37.32	529	9.65
(No R. I. reports)												
Massachusetts	707	29.32	1303	54.04	797	33.05	61	2.53	858	35.58	250	10.36
Indiana	561	19.19	1428	48.85	1198	40.98	105	3.59	1303	44.57	192	6.56
Wisconsin	383	20.52	954	51.12	748	40.08	51	2.73	799	42.81	113	6.05
Maine	352	19.31	888	48.72	623	34.19	89	4.88	712	39.07	222	12.18
New York	212	33.17	434	67.91	137	21.43	15	2.34	152	23.78	53	8.29
Maryland	565	28.72	980	49.82	461	23.43	162	8.23	623	31.67	364	18.50

CHART A (*Continued*).

	Total of ℞'s with Proprietaries. Number.	Per Cent.	Total of One-ingredient ℞'s. Number.	Per Cent.	Total of Several-ingredient ℞'s. Number.	Per Cent.	Total Number of ℞'s.	Per Cent. of Total Number ℞'s.
United States	12,645	52.12	15,276	62.97	8983	37.03	24,259	100
New England (No R. I. reports)	2574	46.97	3499	63.86	1980	36.13	5479	100
Massachusetts	1108	45.94	1393	57.77	1018	42.21	2411	100
Indiana	1495	51.14	2065	70.64	858	29.35	2923	100
Wisconsin	912	48.87	1319	70.68	547	29.30	1866	100
Maine	934	51.25	1159	63.60	663	36.37	1822	100
New York	205	32.08	359	56.18	280	43.81	639	100
Maryland	987	50.17	876	44.53	1091	55.46	1967	100

CHART B.

	All Classes of Customers. Number of States Reporting.	Number of Stores Reporting.	Number of.	Per Cent of.	Number of ℞'s from.	Average ℞'s per Customer.	Per Cent of ℞'s from.	Number of ℞'s per Day.	Number of ℞'s per Week.	Number of ℞'s per Month.
United States	27	68	19,915	100	23,665	1.18	100	11.60	81.20	348.01
New England (No R. I. reports)	5	20	3999	100	4730	1.18	100	7.88	55.18	236.50
Massachusetts[1]	1	12	2240	100	2770	1.23	100	7.69	53.85	230.83
Indiana	1	7	2656	100	3175	1.19	100	15.11	105.83	453.57
Wisconsin	1	7	1660	100	1875	1.12	100	8.92	62.49	267.85
Maine	1	5	1078	100	1211	1.12	100	8.07	56.51	242.20
Maryland	1	4	1807	100	1976	1.09	100	16.46	115.26	494.00
New York	1	4	479	100	574	1.20	100	4.78	33.48	143.50

[1] Only states with four or more reporting drug stores are here analyzed.

CHART B (*Continued*).

	One-Prescription Customers.						Two-Prescription Customers.					
	Number of.	Per Cent of.	Number of ℞'s from.	Daily Frequency (Av. Store).	Frequency in Customers.	Per Cent of Tatal ℞'s from.	Number of.	Per Cent of.	Number of ℞'s from.	Daily Frequency (Av. Store).	Frequency in Customers.	Per Cent of Total ℞'s from.
United States	16,681	83.76	16,681	8.17	1:1.18 (6 in 7)*	70.48	2741	13.76	5482	1.34	1:7.26 (4 in 29)	23.16
New England (No R. I. reports)	3364	84.11	3364	5.60	1:1.18 (6 in 7)	71.12	544	13.62	1088	0.90	1:7.35 (3 in 22)	23.00
Massachusetts	1792	80.00	1792	4.99	1:1.25 (4 in 5)	64.69	370	16.51	740	1.02	1:6.05	26.71
Indiana	2217	83.47	2217	10.55	1:1.19 (5 in 6)	69.82	360	13.55	720	1.71	1:7.39 (5 in 37)	22.67
Wisconsin	1464	88.19	1464	6.97	1:1.13 (8 in 9)	78.08	178	10.72	356	0.84	1:9.32 (3 in 28)	18.98
Maine	956	88.68	956	6.37	1:1.12 (8 in 9)	78.94	112	10.38	224	0.74	1:9.62 (3 in 29)	18.49
Maryland	1650	91.31	1650	13.75	1:1.09	83.50	145	8.02	290	1.20	1:12.46 (2 in 25)	14.67
New York	394	82.25	394	3.28	1:1.21 (5 in 6)	68.64	75	15.65	150	0.62	1:6.38 (3 in 19)	26.13

* Round figure averages.

CHART B (*Continued*).

	Three-Prescription Customers.						Four-Prescription Customers.					
	Number of.	Per Cent of.	Number of R's from.	Daily Frequency (Av. Store).	Frequency in Customers.	Per Cent of Total R's from.	Number of.	Per Cent of.	Number of R's from.	Daily Frequency (Av. Store).	Frequency in Customers.	Per Cent of Total R's from.
United States	470	2.36	1410	0.23	1:42.3 (3 in 127)	5.95	23	0.11	92	0.011 (1 in 89 days)	1:865.7[a]	0.38
New England (No R. I. reports)	86	2.15	258	0.14	1:46.5 (2 in 93)	5.45	5	0.12	20	0.008 (1 in 121 days)	1:799.8	0.42
Massachusetts	74	3.30	222	0.20	1:30.2 (5 in 151)	8.01	4	0.17	16	0.011 (1 in 89 days)	1:560.0	0.57
Indiana	78	2.93	234	0.37	1:34.0	7.37	1*	0.03	4	0.004 (1 in 212 days)	1:2656*	0.12*
Wisconsin	17	1.02	51	0.08	1:97.6 (2 in 195)	2.72	1*	0.06	4	0.004	1:1660*	0.21*
Maine	9	0.83	27	0.06	1:119.7 (3 in 359)	2.22	1*	0.09	4	0.006 (1 in 152 days)	1:1078*	0.33*
Maryland	12	0.66	36	0.10	1:150.5 (2 in 301)	1.82	None	0	0	0	0	0
New York	10	2.09	30	0.08	1:47.9 (1 in 48)	5.22	None	0	0	0	0	0

* Since but one customer is present, the results are not representative ratios and per cents.

[a] Equivalents in round figures.

THE ASSISTANT PHARMACIST.*

BY J. G. BEARD.[1]

At the 1926 convention OF THE AMERICAN PHARMACEUTICAL ASSOCIATION I served as Chairman of the Section on Education and Legislation. My address was lengthy and highly statistical. It dealt entirely with the subject of assistant pharmacists, historically and numerically. It was published on page 1119 of the December 1926, issue of the JOURNAL OF THE A. PH. A. In all due modesty I can recommend to those who are concerned with the question a thoughtful study of the facts there set forth in order to ascertain the ideas of that time and the conditions that then obtained.

In the data presented it was shown that thirty-six states permitted the licensing of assistants and that approximately 20,000 assistants were registered. It was further stated that the grade began in 1870 when Maine and Rhode Island established two types of licentiates.

Although exact figures cannot be determined by me at this time, I was advised a few weeks ago that only "fifteen or sixteen states now permit the licensing of assistant pharmacists and that in four or five of these some educational requirements are compulsory." It follows, therefore, that in the thirteen years since 1926 twenty-two states have abolished the original licensing of assistants.

In my address referred to above I recommended that the A. PH. A. go on record as favoring the abolishment of assistant pharmacist examinations. This recommendation was favored by the Section on Education and Legislation in the following language:

"Resolved, that the recommendation contained in the address of the Chairman, with reference to principles of sub-standard registration is hereby approved and adopted, which recommendation is as follows:

"In the light of the foregoing facts and arguments, and particularly in view of the action of the National Association of Boards of Pharmacy last year, it is here recommended that the Section on Education and Legislation of the AMERICAN PHARMACEUTICAL ASSOCIATION go on record as opposing the principle of sub-standard registration and that it use its influence along with the Boards in bringing about the ultimate discontinuance of the grade of 'Assistant Pharmacist.' "

The above resolution was referred to the House of Delegates and was adopted. Please refer to page 1022, December 1926, JOUR. A. PH. A.

Thus we see that the first organized stand against assistants was taken by the N. A. B. P. in 1925 and by the A. PH. A. in 1926.

. . . . . .

It is pertinent in this year of 1939 to ask this question: Where Do We Go from Here in Respect to Assistant Pharmacists?

The next ten years will determine whether we are to maintain a four-year course of study as a prerequisite for a single type of licentiate, or whether, under the intense pressure of a demand that the stores now in existence or to be estab-

* Presented before the Section on Education and Legislation, A. PH. A., Atlanta meeting, 1939.

[1] Dean, School of Pharmacy, Univ. of N. Car., Chapel Hill, N. Car.

lished later be kept manned by some sort of licentiate, we are forced to retreat to conditions that will hold back the educational progress of American Pharmacy for an unpredictable number of years.

The fate of all prerequisite legislation will rest, in the final analysis, in the hands of state associations, but bodies such as the one here assembled and the national associations concerned with the matter must bear the burden of leadership and of education. The program of mass endeavor must be coördinated properly or else the fight is lost.

EARLY RELATION OF PHARMACY AND MEDICINE IN THE UNITED STATES.*

F. E. KREDEL[1] AND J. HAMPTON HOCH.[1]

In the British colonies, which later became the United States, little distinction obtained between the professions of Pharmacy and Medicine until the time of the Revolution. Diagnosing disease and treating the sick as well as compounding and vending drugs were carried out by the same individual, usually called "doctor," although in nine cases out of ten he did not possess a medical degree.

There were several reasons for this state of affairs. The hard life in the colonies did not attract many qualified practitioners of either art to settle here. Many of those who emigrated in the seventeenth century soon returned to the easier life of the mother country. Because of the dearth of qualified men "anyone who knew calomel from tartar emetic, jalap from ipecac, and had the assurance to use them, who could make and apply ointments and plasters, dress wounds or splint a broken limb, was a welcome settler and received the title of doctor without asking." Many men of prominence, including governors, preachers, school teachers, commodity dealers and editors, dabbled as physician-apothecaries. As late as 1776 only about 400 of an estimated total of 3500 practitioners of medicine in the American Colonies held degrees.

Most of the early settlers came from England where the prerogatives of physician and apothecary were not as well defined as on the Continent. Rolleston (1) has noted that the Paris Society of Apothecaries was granted a separate coat of arms in 1629 and their quarrel with the physicians died down, at least temporarily. In 1688 in Belgium the dispute between the pharmacists and medical practitioners culminated in a law forbidding physicians to dispense their own prescriptions. In England, however, the long controversy between the College of Physicians and the Society of Apothecaries[2] continued well into the eighteenth century and the activities of the apothecaries as practitioners increased during this period. Their standing with the public had been enhanced by their steadfast services during the plague year of 1665 when many physicians deserted London and followed wealthy patients to the country.

Records of the earliest years reveal that few physicians came to the colonies to establish practices on their own initiative. Surgeons and physicians did contract

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* Presented before the Section on Historical Pharmacy, A. PH. A., Atlanta meeting, 1939.

[1] From the Department of Surgery and the School of Pharmacy of the Medical College of the State of South Carolina.

[2] The Apothecaries were separately incorporated by James I in 1617.

their services to the trading and colonizing companies or proprietors for varying periods and a few ships' surgeons remained in the colonies. These men perforce prepared their own medicines; apothecaries were even scarcer than physicians and surgeons. Regardless of the label he bore—whether "physitian," "chirurgeon" or "poticary"—the practitioner served in all categories.

With the advent of new settlers, the birth of new generations and the evolution of a more stable form of life in the colonies, populous cities arose and the earlier primitive medical practices slowly passed. Increasing numbers of physicians, surgeons and apothecaries established themselves in the population centers and undertook the instruction of apprentices in the art and mystery of their calling. After a few years' apprenticeship to a physician or apothecary the young man might set up in business for himself, vending drugs and compounding medicines, or he might conduct an apothecary shop for some physician. Others continued their studies with a physician or surgeon and ultimately became practitioners themselves. The apprentice method of practical training helped to blunt any sharp distinction between Medicine, Surgery and Pharmacy and, since relatively few apprentices finished their education abroad, the European attitude of exclusive privilege and definite boundaries for each profession did not gain general acceptance here until late in the eighteenth century. Even the line around quackery was not clearly drawn. Sigerist (2) suggests that, "we hear little of quacks, probably because," in small communities, "every one knew every one else, and the good or bad results of treatment could not long be hidden."

The practitioner of the combined professions was restricted by few legal enactments. "Immoderate and excessive rates and prices exacted by practitioners in physick and chirurgery" for their services and "druggs and medicines" led Virginia to pass one of the earliest restrictive laws in 1639 and ten years later Massachusetts prohibited all but recognized and tried practices on the part of "chirurgeons, midwives, physitians or others" (3). A code of laws for New York, New Jersey, Martha's Vinyard and Nantucket (1665) contains a section almost identical with the Massachusetts regulation. Virginia enacted a fee bill in 1736 which clearly recognized the difference between surgeons and apothecaries who had only been through apprenticeships and "those persons who have studied physic in any university and taken a degree therein" (4). In 1748 Virginia also forbade "any negroe, or other slave" to "prepare, exhibit or administer any medicine whatsoever" and an enactment of 1751 in South Carolina made it unlawful "for any physician, apothecary or druggist to employ any slave in the shops or places where they keep their medicines or drugs" (5).[1]

The dual status prevailing at the middle of the eighteenth century, even in cities like Philadelphia and Charlestown, is well exemplified in the following: "Rules . . . of the Pennsylvania Hospital . . . practitioners . . shall enter in the said book the recipes or prescriptions they *make* for each of them (patients);" the Faculty of Physic at Charlestown resolved (1755) that "neither can they think that the payment of an apothecary's bill a sufficient reward to him who acts in the three different offices of physic, surgery and pharmacy."

[1] Common usage of the time usually restricted the designation *apothecary* to one who compounded and dispensed medicines at retail, whereas a *druggist* was an importer who sold at wholesale.

Although the colonial physician was necessarily an apothecary, it was still exceptional to find him maintaining a shop for filling other practitioners' prescriptions. One such establishment, founded about 1753 in Reading, Pa., was that of Adam Simon Kuhn. A newspaper advertisement of 1759 relates that, "he has reopened his Apothecary in Reading, which he was compelled to close owing to the fact that he had been unable to engage an efficient representative, and . . . he is in a position to fill in the best and most efficient way, all and every receipts and other prescriptions of the most learned Doctors, through Daniel Adam Kurrer, the well-known druggist who has been in partnership with him in Reading. The Apothecaries in Lancaster and Reading will stay in constant correspondence with each other and will be managed with utmost care by persons who are well-versed in the science of Pharmacy" (6).

Benjamin Franklin, as secretary to the Board of Managers of the Pennsylvania Hospital reported that, "The practitioners charitably supplied the medicines gratis till December 1752, when the managers, having procured an assortment of drugs from London, opened an apothecary's shop in the hospital; and it being found necessary, appointed an apothecary to attend and make up the medicines daily, according to the prescriptions, with an allowance of fifteen pounds per annum for his care and trouble" (7). The first apothecary, Jonathan Roberts, resigned in 1755 to accept more remunerative employment and was succeeded by John Morgan, then an apprentice of Dr. John Redman, who served for a little over one year. A little later (1766) the Pennsylvania Hospital agreed to instruct Thomas Boulter in the "art, trade and mystery of an apothecary." Morton (8) reproduces the articles of this apprenticeship.

The trend toward separation of the practice of Pharmacy from that of Medicine, then, is clearly evidenced in America in the decades before the Revolution. Increased acceptance of the advantages and desirability of such a separation can largely be attributed to the greater number of Americans who completed their medical training abroad and returned to the colonies imbued with the prevailing European viewpoint. The Virginia Club of Edinburgh, composed of medical students from the colony of Virginia, bound every member "for the honor of his profession, not to degrade it by hereafter mingling the trade of an apothecary or surgeon with it." They even petitioned the Virginia House of Burgesses in 1761 to require proper licensing of all practitioners, who should hold a doctor's degree. Also, the emigration of numerous physicians, surgeons and apothecaries from various countries and principalities brought to our shores men trained according to the European systems in which Pharmacy was a separate profession. Dr. Lewis Mottet, a native of France, proposed in 1769 the establishment of a pharmaceutical institute for South Carolina, to correct the common irregular methods of practice (9).

These first indications of the cultivation of Pharmacy as a profession distinct from Medicine were markedly intensified by John Morgan. After completing his medical studies abroad, he returned in 1765 to found the Medical School of the College of Philadelphia and became the outstanding advocate of the separation of Pharmacy and Medicine. His remarks (10) on this subject have been widely quoted.

"The paying of a physician for attendance and the apothecary for his medicines apart, is certainly the most eligible mode of practice, both to patient and practitioner. The apothecary

then, who is not obliged to spend his time in visiting patients, can afford to make up medicines at a reasonable price; and it is as desirable, as just in itself, that patients should allow fees for attendance, whatever it may be thought to deserve. They ought to know what it is they really pay for medicines, and what for physical advice and attendance.

"We must regret that the very different employment of a Physician, Surgeon, and Apothecary should be promiscuously followed by any one man, however great his abilities. They certainly require very different talents.

"The business of Pharmacy is essentially different from either. Free from the cares of both, the Apothecary is to prepare and compound medicines as the Physician shall direct. Altogether engaged in this, by length of time he attains to that nicety of skill therein which he never could have arrived at, were his attention distracted by a great variety of other subjects."

Since physicians often derived the greatest part of their incomes from their medicines rather than from their services, Morgan was attacking the financial basis of American medical practice. Scant wonder his recommendations were not immediately accepted. In keeping with his resolve to get his living "without turning apothecary or practitioner of surgery," and because he believed that an apprentice could not be a good pharmacist, Morgan brought an English trained pharmacist, David Leighton, back to Philadelphia with him and sent his prescriptions to Leighton to be filled. The innovations introduced by John Morgan undoubtedly stemmed from his associations in Edinburgh (11) and the course he pursued sanctioned the independent existence of the profession of Pharmacy (12). A few physicians in Philadelphia, notably Dr. Abraham Chovet in 1770 and Dr. John Jones in 1780, followed Morgan's example and adopted the plan of writing prescriptions for their patients.

The practice of Pharmacy was gradually and achingly becoming detached from the practice of Medicine, but the separation had only started when the Revolutionary War opened. The recognition of the apothecary as an office distinct from the physician and surgeon was given added impetus by various enactments, of provincial congresses and of the Continental Congress, relating to the organization of the army. Provision for an apothecary-general and apothecary mates was made in the plan adopted in 1775 and was continued in the reorganizations of 1777 and 1780. Shops and laboratories were specially designated for the preparation of drugs and compounding of medicines to be distributed to the various hospitals and field units. The first American pharmacopœia (1778) was prepared particularly for use in the army hospitals. The travel, associations and varied experience gained in the medical department of the army undoubtedly widened the outlook of many practitioners and sent them back to civil life with a new realization of the apothecary's rôle in improved medical service.

In the latter part of the eighteenth century the customary combination of physician and pharmacist continued in most cases and contemporary newspaper notices, in which physicians and apothecaries advertised their wares, reveal a very keen, oft times bitter, trade competition. DeWarville in 1788, in his "New Travels in the United States of America," says: "The greater part of these physicians are at the same time apothecaries. They continue to unite the two sciences, out of respect to the people, who wish that the man who orders the medicine should likewise prepare it. There are, however, other apothecaries, of whom the physicians purchase their drugs." Public demand (?) for continuing this dual status was, however, probably a less powerful incentive than the profit to be derived from the

sale of drugs. In fact, partnerships were often formed between the physician and the apothecary with resultant division of labor, but without sacrifice of drug profits on the physician's part. This arrangement which was superior to the earlier custom has persisted in some cases to the present time.

After the Revolution, when knowledge of European advances became more widespread, medical practices improved; state medical societies were formed, dispensaries were established, and licensure laws were passed. These developments were a forward step in the evolution of Pharmacy as a separate profession. When dispensaries for supplying free medical care to the poor were opened in Philadelphia (1786), New York (1791), Charleston (1798) and other cities, an apothecary was usually appointed in order to provide adequate pharmaceutical service. Following the earlier regulations of New York (1760) and New Jersey (1772), state legislatures of the new Republic generally placed the licensing of medical practitioners in the hands of medical societies or boards of examiners[1] (13). In some instances the pharmacist was included in these regulatory acts. For a few years (1786–1790) Virginia levied a license tax on every practising physician, surgeon and apothecary. However, the first pharmacist to stand an examination before a licensing board was Richard Johnson, who on December 14, 1818 was quizzed by four members of the Medical Society of South Carolina (14).

Although medical colleges gave instruction in pharmaceutical subjects as a part of the medical course at an earlier date, it was not until 1821 that the first college of pharmacy was founded by the apothecaries and druggists of Philadelphia and not until 1826 that the first class was graduated. The University of Pennsylvania had considered (1819) establishing a curriculum for pharmacy students and the Faculty of Medicine in 1821 nominated sixteen men for honorary degrees (Master of Pharmacy). This "unwarrantable assumption of power on the part of the University and injudicious innovation in academical practice" stirred the local druggists and apothecaries to establish their own college. By providing opportunity for formal education, eradicating injurious practices, formulating a code of professional conduct and assuming responsibility for forwarding the interests of Pharmacy this college did much to advance the character of the profession and establish it on a firm basis as a separate entity (15). The organization of an association by the apothecaries of Boston in 1823 and the establishment of colleges of pharmacy in New York (1829), Maryland (1841), Cincinnati (1849) and Boston (1850) extended the autonomy of Pharmacy.

REFERENCES.

(1) Rolleston, H., "The Historical Relations of Pharmacy and Physic," *Pharm. J.*, 139, 391 (1937).

(2) Sigerist, H. E., American Medicine (1934).

(3) Packard, F. R., "History of Medicine in the United States" (1931).

(4) Blanton, W. B., "Medicine in Virginia in the Eighteenth Century" (1931).

(5) Hoch, J. H., "Early History of Pharmacy in South Carolina," *Southeastern Drug J.*, 8, 3 (1934).

(6) Gibson, J. E., "Dr. Bodo Otto and the Medical Background of the American Revolution" (1937).

[1] Mass. (1781), N. H. (1791), Conn. (1792), Md. (1799), N. Y. (1806), N. J. (1816), Ind. (1816), S. C. (1817), Del. (1819), D. C. (1819), Vt. (1820), Ohio (1820), La. (1820), Me. (1821), Ala. (1823), Ga. (1826), Miss. (1829), etc.

(7) Wilbert, M. I., "The Beginnings of Pharmacy in America," *Am. J. Pharm.*, 79, 400 (1907).

(8) Morton, T. G., and Woodbury, F., "The History of the Pennsylvania Hospital 1751–1895" (1895).

(9) Hoch, J. H., "Dr. Lewis Mottet's Projected Institute of Pharmacy (1769)," JOUR. A. PH. A., 27, 1260 (1938).

(10) Morgan, John, "A Discourse upon the Institution of Medical Schools in America" (Reprint from first edition, 1765), (1937).

(11) Wilbert, M. I., "Benjamin Franklin," etc., *Am. J. Pharm.*, 78, 214 (1906).

(12) Norris, G. W., "The Early History of Medicine in Philadelphia" (1886).

(13) Shafer, H. B., "The American Medical Profession, 1783 to 1850" (1936).

(14) Hoch, J. H., "The First American Board of Pharmacy," *Am. J. Pharm.*, 104, 752 (1932).

(15) England, J. W., Ed., "The First Century of the Philadelphia College of Pharmacy, 1821–1921" (1922).

CIRCULARS ISSUED BY THE BUREAU OF NARCOTICS.

During the twelve-month period ending June 30, 1939, the number of thefts of narcotic drugs from the premises of persons registered under the federal narcotic laws reached a total of 733 as compared with a total of 657 during the previous year.

This sharp increase in the number of such thefts reported leads this office to again issue a warning that increased caution should be exercised in the handling of narcotics, and to reiterate its insistence that stocks of such drugs be provided with secure places of storage.

That the addict and peddler turn more and more to the robbing of legitimate stocks as the supply of illicit drugs becomes more restricted is a fact of experience. Opium, morphine, dilaudide, cocaine and even codeine and dionin are highly attractive to such persons. Such drugs should always be stored in safes or strongly constructed vaults, and where the stocks are of considerable size, some type of electrical protection for the premises is also recommended.

Article 193 of Regulations No. 5 requires that narcotic drugs and preparations shall at all times be properly safeguarded and kept secure. In every case, whatever measures are required by the circumstances and surroundings should be taken. Manufacturers and wholesale dealers, who constitute the source of supply for other registrants and who are generally known to carry substantial stocks of narcotics, should be especially alert to see that their stocks are fully protected. . . . . .

It has come to the attention of the Bureau that due to the European situation there is some uneasiness in certain quarters of the drug trade regarding a possible shortage of narcotic items, and that this is prompting some registrants to make purchases beyond their normal requirements.

Due to the importing and storing of opium reserves in customs warehouses, a policy initiated several years ago, there are now adequate supplies of raw opium and finished opium derivatives within this country to supply all normal needs for approximately three years.

There is accordingly no occasion for fearing a shortage of such drugs, and in order that the machinery of orderly distribution may not be disrupted, this office will appreciate the coöperation of the trade in limiting all transactions in such items, both purchases and sales, to normal requirements for immediate needs.

The accumulation of excess stocks on the shelves of retailers and practitioners results in theft hazards. Manufacturers and wholesale dealers are therefore urged, not only to limit their own purchases to normal manufacturing and distribution needs, but also to refrain from sales drives, and the offering of price discounts for quantity orders or any other concession which might operate as an inducement to registrants to purchase beyond their actual requirements.

Several years ago there was a temporary dislocation of codeine stocks due to a false fear of a general shortage, wholly unwarranted by the actual condition of stocks. The Bureau desires to avoid a recurrence of this situation without the necessity of requiring monthly stock inventories and the institution of a quota system, and desires your active coöperation to this end.

H. J. ANSLINGER, *Commissioner*.

PROCEEDINGS OF THE LOCAL AND STUDENT BRANCHES

ALABAMA POLYTECHNIC INSTITUTE STUDENT BRANCH.—The first regular meeting of the year was opened September 11th, at eight o'clock by President Hiller, who then welcomed both the old and new students. Each was called upon to stand and introduce himself by giving name, home town and class.

President Hiller called on the members of the Pharmacy faculty to say a few words. Dr. Blake, after welcoming the new students, explained the organization and purpose of the Student Branches of the A. PH. A., giving some of their accomplishments. Our faculty adviser, Professor Hargreaves, listed some of the advantages of membership in the A. PH. A. and urged the full coöperation of all students in the work of the Student Branch.

Professor Nickel welcomed the new students and followed up the remarks of Professor Hargreaves.

In the absence of Mr. Thaggard, delegate to the A. PH. A. convention, President Hiller read a written report of the convention of the A. PH. A., held in Atlanta during August.

Mr. Eich suggested that the Student Branch sponsor a dance sometime during the year. This met with approval of the members and President Hiller announced that he would obtain a suitable date for same.

Mr. Croxton suggested that the department get busy on plans for the inspection trip. President Hiller then appointed a committee, consisting of Messrs. Croxton, Bozeman and Lurie to assist Dr. Blake in making preparations for the trip.

Professor Nickel stated that it had been the policy of the society to make several displays during National Pharmacy Week and have one night set aside as Pharmacy night. He suggested that a committee be appointed to look into this matter. Messrs. Eich, Barron and Pittman were appointed on this committee.

BEN EICH, *Secretary.*

BALTIMORE.—The initial fall meeting of the Branch was held at the School of Pharmacy, University of Maryland, on Thursday evening, October 5th. This was a joint meeting with the Baltimore Retail Druggists Association and Branch members and friends were urged to help make the occasion an outstanding meeting to inaugurate the 1939–1940 season.

The guest speaker for the evening was Dr. D. M. Copley, of the Norwich Chemical Company. Dr. Copley presented a talk on vitamins from the viewpoint of the pharmacist.

A report on the recent annual A. PH. A. meeting held in Atlanta was presented at this meeting.

Refreshments were served at the conclusion of the session.

ROBERT S. FUQUA, *Secretary.*

RHODE ISLAND COLLEGE OF PHARMACY AND ALLIED SCIENCES STUDENT BRANCH.—The April meeting was held on the 13th, President Lawrence Bartley presiding. Attendance was 100%.

Appointments to the committees under the Constitution were voted to be withheld until the beginning of the next college year in September 1939, due to the short period of time the appointees would have to serve for the remaining college year. The official pins of the association were distributed to members by Secretary Stadnik.

A discussion followed relative to the conducting of a May-Day Festival, to which all the college would be welcome. Members finally decided to hold it May 1st at the Lincoln Reservation. Through the coöperation of Dean Rivard and Prof. Fitz Simon, the college closed at 12.00 M. the day of the Festival. The members of the committee for the Festival were to be chosen and posted and the chairman was instructed to consult members of this group.

. . . . . .

The May meeting was called to order on the first. The committee gave brief reports of their activities. The short meeting adjourned until afternoon at Lincoln Woods Reservation, the site of the May-Day Festival. Lawrence Bartley, president, presided.

All members of the college were invited and a large number attended, where a hot dog roast, sporting events and a ball game followed. Dr. Church, of the Pharmacology Department, lent a hand to the occasion by conducting a field trip through the reservation and gave an interesting talk to the group.

Prizes were awarded to winners of the different events by Professor Hickey of the Pharmacy Department and Professor Crombie of the Bacteriology Department. Members of the Student Branch acted as constituents of the different committees which functioned so successfully. This is the type of activity, combined with educational talks and discussions, we of the Branch intend to constitute our future endeavors.

JOHN STADNIK, *Secretary.*

THE ASSOCIATION FOR THE ADVANCEMENT OF PROFESSIONAL PHARMACY.

The importance of proper observance of National Pharmacy Week was the subject of discussion at the first fall meeting of the Association for the Advancement of Professional Pharmacy held September 26th at the Hotel Empire, New York City.

Members were urged to put their best efforts behind the Week in the form of proper worthwhile displays and advertising. The need for bringing the Professional side of Pharmacy before the public and raising of the standards of the profession so as to make it attractive to the new highly professional type of Pharmacy College graduate were stressed by Dean Charles W. Ballard of Columbia University, College of Pharmacy.

An inspiring talk on the Atlanta Convention and the future activities of the A. PH. A. was given by Dr. J. Leon Lascoff. Dr. Lascoff reported on the great success of the newly organized Conference on Professional Pharmacy under the Chairmanship of Dr. C. B. Jordan, Dean of the College of Pharmacy of Purdue University, and stated that they planned another Conference at Richmond, Va., next year.

Dr. Curt P. Wimmer, Professor of Pharmacy of Columbia University College of Pharmacy, spoke on the "Future of Pharmacy." He stated that with the present four-year course for pharmacists, we may look forward to great advances in the Profession of Pharmacy.

To assist the members and guests in bringing their prescription equipment up to date displays of pharmaceutical glassware, prescription packages and other equipment were prepared by Whitall Tatum, Owen Illinois and Pictorial Paper Package Co. Prescription balances were displayed by Troemner. Numerous pharmaceutical publications and textbooks were made available by Barnes and Noble for examination by members. The members were also given a preview of the new National Pharmacy Week window display to be used this year which is available through manufacturers, if requested.

The next meeting of the Association will be held during National Pharmacy Week on October 24th at the Hotel Empire. The program will be dedicated to the observance of National Pharmacy Week. Members have been urged to submit photographs of their National Pharmacy Week displays for exhibition during the meeting.

HELP STAMP OUT TUBERCULOSIS.

In our world of tomorrow each one of us would want to reduce suffering and illness to the least possible minimum. At this time of year we have an opportunity to be practical about that desire. It is one thing to wish and another to do. Our world of to-day is still struggling against a powerful enemy—tuberculosis. Tomorrow's world need have none of it, if we have a real desire to conquer it.

Christmas Seals are the means by which the National Tuberculosis Association and its 2000 state, county and city organizations throughout the United States, Alaska, Puerto Rico and Hawaii carry on their year-round battle against tuberculosis. Seals may be ordered from—National Tuberculosis Association, 40 W. 50th St., New York City.

PERSONAL AND NEWS ITEMS.

Dr. P. A. Foote, who for the past eleven years has been Professor of Pharmacy at the University of Florida, has been appointed Acting Director of the School of Pharmacy and Professor of Pharmaceutical Chemistry at that institution.

Dr. F. V. Lofgren, formerly Dean of the School of Pharmacy at Valparaiso University, has been appointed Acting Head Professor of Pharmacognosy and Pharmacology in the School of Pharmacy at the University of Florida.

Dr. C. H. Johnson, who for the past three years has been pharmacognocist for the Upjohn Company, has been appointed Instructor in Pharmacognosy in the School of Pharmacy at the University of Florida. Dr. Johnson will also be in charge of the medicinal plant garden at that institution.

The twenty-fourth annual meeting of the **Federal Wholesale Druggists Association** was held in Hot Springs, Va., recently. Tribute to the memory of Mr. R. E. Lee Williamson, who had served as secretary of the Association since its organization, was paid by the members. Among the speakers were: Keith Keller on "Mutual Problems of the Manufacturer and the Retail Druggist," and Ernest I. Kilcup on "Taxation." Attendance was high, and the entertainment elaborate. Mr. Sidney C. James, of the Ellicott Drug Co., Buffalo, N. Y., was elected president. The selection of a secretary was left to the Executive Committee.

The National Association of Retail Druggists held their annual convention in St. Paul, Minn., October 9th to 13th. Among the speakers were: Senator J. C. O'Mahoney of Wyoming; I. H. Bander, of McKesson & Robbins; Gov. Francis P. Murphy, of New Hampshire; Earle F. Gardemann, secretary of the Utah Pharmaceutical Association; Dr. R. L. Swain, editor of *Drug Topics;* Dr. Alfred P. Haake, National Association of Manufacturers; Congressman Wright Patman of Texas; R. J. Wilkinson, Master Photo Finishers of America; Dr. Ernest Little, dean of New Jersey College of Pharmacy; A. C. Nielson, statistician; J. J. Donlan of the *American Weekly;* and Senator John E. Miller of Arkansas. The convention was record-breaking, and the entertainment features most pleasing, among which was an Ice Carnival.

The **New Hampshire Pharmaceutical Association** met September 10th to 12th at Bretton Woods. The Convention, an All-New England one, was well attended. Among the speakers were: Dr. Chester E. Merror, radio commentator, on "Issues of the Hour;" Dr. Hugh P. Beirne, executive committeeman, N. A. R. D.; Mr. Charles D. Howard, director, New Hampshire State Board of Health Laboratories and editor of *New Hampshire Health News;* H. C. Christensen, secretary, N. A. B. P.; Robert W. Rodman, editor, *Druggists' Circular;* C. R. Metcalf, secretary N. H. Medical Society; E. D. Omohundro, director of McKesson & Robbins Laboratory, on "Problems under the New Food, Drug and Cosmetic Act;" Charles A. Loring, Gilman Brothers, Inc., on "Your Drug Store;" and David A. Bissett, circulation manager, Manchester *Union and Leader,* on "Big Newspaper Distribution Throughout the State."

The Montana Pharmaceutical Association met at Missoula September 25th and 26th. The convention was well attended and was very successful. The significance of the meeting was the forward-looking attitude of every person in attendance. High points of the convention were the dedication of the new Pharmacy-Chemistry building of the Montana State University (Dean Mollett laid the cornerstone); the drawing up and adoption of new by-laws and articles of incorporation for the association; and celebration of the passage of the new Pharmacy Law. Prominent speakers were: Louis Fischl, California druggist; John Bonner, secretary-counsel for the Montana Trade Commission; Harry Kaufman, state supervisor for distributing education for the State Board of Education, and many of the university executive heads. Next year will bring the fiftieth anniversary, and plans are afoot for a most interesting meeting.

The National Wholesale Druggists' Association met in White Sulphur Springs, W. Va., September 24th to 27th. Mr. George V. Doerr, of McKesson & Robbins, Inc., was elected president and E. L. Newcomb was re-elected as secretary. Hon. Homer A. Holt, Governor of West Virginia, made an address; and the presidential address of John C. Davis was marked with optimism and gratification. White Sulphur Springs was again chosen as the meeting place, and the convention will be held during the week of September 30, 1940.

Among those who visited the American Institute of Pharmacy during September are: Emil C. Horn, Milwaukee, Wis.; F. C. Wissler, Niagara Falls, N. Y.; Irving Liebman, Brooklyn, N. Y.; Charles H. Phillips, Daytona Beach, Fla.; Roderick Miller, Carlstadt, N. J.; L. W. Hazleton, Washington, D. C.; E. Stevenson, Corby, Northants, England; Edward Evans, Vandling, Pa.; Margaret Wilson, Washington, D. C.; W. A. Wissler, Niagara Falls, N. Y.; William Perlman, New York City; Ruth Munro, Boulder, Colo., Veta B. Painter, Washington, D. C.; J. Henry, Washington, D. C.; David H. Pucakoff, Brooklyn, N. Y.; G. J. Bushnell, Wethersfield, Conn.; O. S. Rask, Baltimore, Md.; E. H. Hamilton, Washington, D. C.; C. D. Schreiber, Tell City, Ind.; Richard C. L. Nign, Washington, D. C.; Ida A. Jones and Cornelia Jones, Belton, Mo.; Albert Rosencranz, Evansville, Ind.; Mr. and Mrs. Wm. Emrich, Orlando, Fla.; Harry Landis Thompson, Salt Lake City, Utah; Allen Rosencranz, Evansville, Ind.; Elsie L. Backus, Chicago, Ill.; Mrs. Lee H. Pfahler, Savannah, Ga.; Louis Botfeld, Carlton Ave., Central Islip; Fred B. Pfahler, Savannah, Ga.; Edith J. Backus, LaPorte, Ind.

Dr. Robert P. Fischelis, Executive Secretary and Chief Chemist of the Board of Pharmacy of the State of New Jersey, has been appointed a member of the New Jersey State Board of Health. The appointment comes at a time when a new State Food, Drug and Cosmetic Act, similar to the Federal Food, Drug and Cosmetic Act, goes into effect in New Jersey. Because of the more complete control over the manufacture and distribution of drugs, devices and cosmetics provided in the new state law, the legislature amended the State Health Act to add a pharmacist to the Board of Health, and Dr. Fischelis is the first pharmacist to hold this appointment, which is for a four-year term under the amended act.

In a decision handed down by the North Carolina Supreme Court on September 28th, the constitutionality of the North Carolina Fair Trade Act was upheld. The decision reverses the judgment of the lower court which on March 17th was found against Eli Lilly and Co., in its suit against L. S. Saunders of Wilmington. This decision should establish a valuable precedent in other states where the constitutionality of Fair Trade Acts under state constitutional provisions may be questioned.

OBITUARY.

DR. HENRY A. PETERS.

Dr. H. A. Peters, life-long resident of Oconomowoc, Wis., died suddenly July 19th, following an appendectomy. He was the son of Henry M. and Augusta R. Peters. His early education was received in Oconomowoc schools and he was graduated from the University of Wisconsin in Pharmacy in 1892. Later he entered the Milwaukee Medical College where he received his M.D. degree in 1906.

Dr. Peters was a pharmacist at Brown's Pharmacy, the present Stevens' Pharmacy, for sixteen years, prior to his study of medicine, and was appointed to the Wisconsin State Board of Pharmacy in 1903 and served as its president for several years. He was appointed to the faculty of the Milwaukee Medical College in 1903 as instructor in Pharmacy.

He was a member of the Rotary Club, past-president of the Chamber of Commerce, a charter member of the Bachelor Club and served as a member of the board of the Oconomowoc Public Library. He was a member of the American State and Waukesha County Medical societies, and served on committees of the Wisconsin and American Medical Associations. He had been a member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1903.

Dr. Peters is survived by his widow, Mrs. Emma Nicolaus Peters, whom he married in 1918; and three children, Charlotte, Henry, Jr., and Joanne; also two brothers, Otto and Edward, the latter of California.

The offices of the doctors in the city were closed for two hours that the physicians might attend the funeral in a body.

The *Oconomowoc Enterprise* wrote: "He was a man of great love—to his family, to those in distress, to his city and to things beautiful—a love that shone with kindliness and consideration for all with whom he came in contact. For nearly sixty-seven years, on the very ground on which he was born, he served, administering aid to others to the hour when he himself entered the hospital.

"Immeasurable is the great amount of professional services freely given by him. Such was the man that he built into the hearts of all citizens a regard and respect few attain, yet in his modesty he disdained tribute and credit. It was he who pioneered the organization of Oconomowoc's Rotary Club, became

its first president and lived according to its ideal of 'Service above Self.' He loved to speak of the city as his own, and it was.

"Seldom is there such a character, a mellowing from achievement in a life devoted to service. There should be comfort for those close to him for having enjoyed him in life. Step by step he accomplished finer things. A great heart, filled with charity and modesty, was his."

BOOK NOTICES AND REVIEWS.

Accepted Dental Remedies (1939). Secretary Harold L. Hansen, Council on Dental Therapeutics, states that this edition is similar to those which have geen prepared in the past under the direction of Dr. Samuel M. Gordon, 1930–1938. (For the 1938 report see page 1284, JOURNAL A. PH. A.) The number of articles listed and described in this volume is considerably larger than in previous editions. Acceptance of a remedy is not an endorsement; the duration varies as to time and may be reconsidered; dentifrices are listed for one year; the rules have been adopted primarily with the object of protecting the dental profession and the public against fraud or imposition, undesirable secrecy and objectionable advertising.

"Accepted Dental Remedies" is a necessary publication for the dentist and a useful book for the pharmacist; it contains more than 300 pages and the price is $1.00 per copy; published by the American Dental Association, 212 E. Superior St., Chicago, Ill.

The use of certain portions of the text of the U. S. P. XI, and of N. F. VI has been granted, and the Council on Pharmacy and Chemistry of the American Medical Association to use portions of the publications, Useful Drugs and New and Non-Official Remedies. Dentifrices are listed, their composition discussed and the names of manufacturers are given, also a list of dentifrices that are not acceptable and some that have been disapproved by courts. The composition of dyes, essential oils and related products is discussed; also mouth washes; cocaine and other local anesthetics are given consideration, followed by various formulas, a biographical index to proprietary and unofficial articles not included in "Accepted Dental Remedies," index to distributors and a general index.

Discovery of the Elements. By MARY ELVIRA WEEKS, Associate Professor at the University of Kansas. The illustrations have been collected by F. B. Dains, Professor of Chemistry. The book was published by the *Journal of Chemical Education*, Easton, Pa., Mack Printing Company being the printers. Price, $3.50; 470 pages.

The book is interesting because of the presentation of the history of the discoverers of the elements together with illustrations of the individuals and events in their lives. In a number of instances there were several who contributed to the discoveries in one way or another; others made discoveries of the same element, independently. Search is shown of the author and coöperators in old journals and reports, and the desire of the author to give proper credit to co-workers of the various periods. The author acknowledges assistance of those mentioned and of Dr. E. H. S. Bailey, Dr. Selma Gottlieb Kallis and Dr. Max Speter. It is interesting to note the lead to the discoveries and the desire of the author and coworkers to be fair in their conclusions. In the "Contents" the periods are grouped when the discoveries were made and give helpful points of study for the reader's guidance, for example only: Elements known to the ancient world, those known to alchemists, elements isolated with the aid of potassium, some elements predicted by Mendeleef, etc. For some of the discoverers it was impossible to show a picture, and instead some event in their lives is given, as an example: an autograph of Bernard Courtois is made use of and his birthplace; the number of those which it was possible to present, evidences a large collection and the activities in connection with the discoveries add interest.

The abundant "Literature Cited" gives leads for study and the mention here may develop in the readers the desire to see a copy of the book; the illustrations have been well selected and the work of the printer has contributed value to the publication.

Carl Wilhelm Scheele is an outstanding representative of Pharmacy among the discoverers of the elements. The author and associates have rendered a valuable service and brought credit to their Alma Mater by making the many references accessible in readable form to those who search the history of Pharmacy and related subjects.